

Risques à la santé et maladies professionnelles
dans les industries alimentaires

Volume 3 : maladies professionnelles

Jacques Binet

Janvier 1992

Département de Santé Communautaire
de l'hôpital du Haut-Richelieu

WA
487
B564
1992
V.3

F 8414
Vol.3
Ex.2



CENTRE DE DOCUMENTATION

Table des matières

Direction de la Santé publique de la Montérégie
Complexe Cousineau
5245, boulevard Cousineau, bureau 3000
Saint-Hubert, Québec
J3Y 6J8

Remerciements

Liste des tableaux

Introduction

INSTITUT NATIONAL DE SANTÉ PUBLIQUE DU QUÉBEC
CENTRE DE DOCUMENTATION
MONTREAL

1 - Surdit  et autres effets du bruit

Bibliographie

2 - Contraintes thermiques et sant 

2.1 Chaleur

2.2 Froid

2.3 Pr vention, contr le et surveillance m dicale

Bibliographie

3 - Travail post  et travail de nuit

Bibliographie

4 - Probl mes musculo-squelettiques

Bibliographie

5 - Zoonoses

Bibliographie

6 - List riose

Bibliographie

7 - Maladies respiratoires

7.1 Asthme professionnel et rhinite allergique

7.1.1 Méthode et dépistage et surveillance

7.1.2 Examens de la fonction respiratoire

7.1.3 Périodicité des examens

7.2 Asthme des boulangers

7.3 Alvéolite allergique

7.3.1 Manifestations cliniques

7.3.2 Examen clinique et laboratoire

7.3.3 Pronostic

7.3.4 Immunologie et pathologie

7.3.5 Dépistage des alvéolites allergiques

7.3.6 Information et prévention

7.4 Syndrome des poussières organiques

7.4.1 Etiologie potentielle

7.4.2 Diagnostic différentiel

7.4.3 Dépistage et prévention

7.5 Bronchite chronique

Bibliographie

8 - Dermatoses

8.1 Dermatitis irritatives

8.2 Dermatites de contact

8.2.1 Fruits et légumes

8.2.2 Prévention

8.3 Dermatites infectieuses

8.3.1 Virus

8.3.2 Infections fongiques

8.3.3 Infections bactériennes

8.3.4 Prévention des infections

Bibliographie

9 - Maladies dentaires d'origine professionnelle

Bibliographie

10 - Risques chimiques

10.1 Asthme des empaqueteurs de viande

10.2 Bioxyde de carbone.

Bibliographie

Liste des tableaux

Tableau I	-	Liste des causes principales d'asthme dans l'industrie alimentaire
Tableau II	-	Synthèse des aspects médicaux à considérer dans l'asthme des boulangers
Tableau III	-	Substances associées à l'alvéolite allergique
Tableau IV	-	Composition des poussières de grain
Tableau V	-	Prévalence des dermatoses spécifiques chez les travailleurs des abattoirs
Tableau VI	-	Plantes culinaires présentant un risque de dermatite de contact

Maladies
respiratoires

7 - MALADIES RESPIRATOIRES

7.1 - Rhinite allergique et asthme professionnel

L'asthme est une condition caractérisée par une hyperexcitabilité de la trachée et des bronches due à des stimuli variés et se manifestant par un rétrécissement réversible diffus des voies aériennes qui varie en gravité soit spontanément soit suite à un traitement.

L'asthme professionnel est une forme d'asthme qui se trouve déclenché suite à des expositions à des aérosols, des poussières, des gaz, des vapeurs, des fumées etc... dans le milieu de travail (tableau I).

7.1.1 Méthode de dépistage et surveillance

Nous avons inclus en annexe le guide de surveillance pour l'asthme professionnel préparé pour le territoire du DSC du Haut-Richelieu. Le guide n'est pas spécifique au domaine de l'alimentation.

L'utilisation d'un questionnaire de dépistage de l'asthme est un outil acceptable même s'il n'est pas encore standardisé. Selon Lebowitz un questionnaire auto-administré peut souvent fournir des résultats satisfaisants à condition qu'il soit complètement rempli. Il est recommandé de l'administrer en début d'emploi pour établir une ligne de base individuelle dans l'évolution des symptômes.

L'examen physique se fait souvent à la suite d'un questionnaire positif et doit être pratiqué à la période où les symptômes se présentent. C'est aussi une bonne occasion pour le médecin de procéder à un questionnaire médical traditionnel, beaucoup plus précis pour orienter le diagnostic.

Les causes d'asthme les plus importantes dans l'industrie alimentaire sont principalement reliées au contact avec des animaux, des produits végétaux, des champignons (tableau I)

Tableau I - Liste des causes principales d'asthme dans l'industrie alimentaire

Produits animaux :	poulets oiseaux comestibles crabes crevettes huîtres oeufs insectes mites de grain
Produits végétaux :	poussières de grain farine de blé farine de seigle farine de sarrasin thé café tabac houblon fèves
Champignons:	Alternaria tenuis Aspergillus clavatus spores de champignons etc...
Produits chimiques:	chlorure de polyvinyle

**Tableau II - Synthèse des aspects médicaux à considérer dans
l'asthme des boulangers**

Réponses à l'inhalation de poussières de grains et de farine - bien toléré - réaction immédiate 10 à 15 minutes après l'exposition - réaction tardive 6 à 8 heures après l'exposition	Allergènes possibles - mites - insectes - moisissures - bactéries - enzymes ajoutés - protéines fongiques - pesticides	Facteurs de risques industriels et personnels - durée d'emploi - assignation à certains postes dans la boulangerie - conditions de travail au poste - antécédents génétiques	Mécanisme des réponses allergiques 1^{er} : libération directe d'un médiateur de contact (v.g. histamine) 2^e : irritation qui entrave une réponse non-immunologique 3^e : réponse immunologique IgE Farine : 3^e mécanisme. Pas d'évidence pour les 2 autres
Distribution des réponses positives aux tests allergiques pour la farine - exposition d'un an : 9% des tests cutanés positifs, mais symptômes chez seulement 5% - exposition de 20 ans : 34% des tests cutanés positifs mais symptôme chez 20% - 91% des boulangers symptomatiques ont des tests cutanés positifs	Difficulté d'évaluation - variété des grains de céréales (composition similaire) : - blé - sarrasin - orge - avoine - riz - maïs - toutes les protéines ne sont pas dans les tests cutanés. (v.g. albumine et globuline le sont mais pas gliodine et glutenide)	Techniques de diagnostic - test cutané - Rast - immunofluorescence avec coloration des grains de blé dans une résine de méthacrylate - essai de libération d'histamine basophile	Diagnostic - histoire - test cutané ou RAST - provocation bronchique - mesures environnementales Diagnostic et prévention - contrôle environnemental - médication - désensibilisation - changement de poste de travail

7.3 - Alvéolite allergique

Meunerie

Sous ce nom on trouve aussi les maladies suivantes : poumon du fermier, pneumonite allergique extrinsèque, poumon du champignoniste, pneumonite granulomateuse, pneumoconiose organique. L'alvéolite allergique est une maladie granulomateuse interstitielle du poumon qui se manifeste suite à l'inhalation répétée de particules de matière organique de 1 à 5 microns chez un sujet prédisposé.

Le prototype de l'alvéolite allergique est le poumon du fermier, mais des études plus récentes mettent en cause bien d'autres produits et quelques-uns se retrouvent dans l'industrie alimentaire (tableau III). Pour cette raison nous avons cru bon d'introduire quelques notions de base qui pourraient servir plus amplement advenant des interventions en milieu agricole. La différence entre l'alvéolite du fermier et celle des autres travailleurs vient de la spécificité des antigènes de chaque produit respiré.

Ces agents partagent cependant en commun une caractéristique qui est la grosseur des particules inhalées qui varient de 1 à 5 microns. Les particules de 1 micron présentent la plus grande probabilité d'atteindre les alvéoles pulmonaires. On présente au tableau III une liste des principales activités reliées directement ou indirectement à l'industrie alimentaire. Les produits en cause sont réputés causer des alvéolites allergiques. Enfin, on ne peut ignorer que les mêmes produits peuvent aussi déclencher des réactions asthmatiques, d'où parfois la confusion au point de vue dépistage et diagnostic.

7.3.1 Manifestations cliniques

Les diverses manifestations cliniques ont les caractéristiques suivantes:

- 50% connaissent un début insidieux
- elles varient selon le niveau d'exposition
- souvent, il y a exposition prolongée à des moisissures, des semaines ou des mois avant la première manifestation
- dyspnée progressive
- 1/3 des attaques sont typiques :
 - frisson
 - toux irritante et harassante
 - dyspnée
 - malaise

Tableau III - Substances associées à l'alvéolite allergique

DISEASE	OCCUPATION	ANTIGEN SOURCE	MAJOR ANTIGENS
	<i>Thermophilic Bacteria and Bacterial Products</i>		
Farmer's lung	Agricultural workers	Moldy hay and grain	<i>Micropolyspora faeni</i> ⁹⁴
Mushroom worker's lung	Mushroom workers	Compost	<i>Thermoactinomyces vulgaris</i> and <i>M. faeni</i> ⁶⁴
Bagassosis	Bagass workers	Moldy sugar cane	<i>Thermoactinomyces sacchari</i> ⁵⁴
Sisal worker's disease	Bag and rope makers	Rope dust	<i>Thermoactinomyces</i> spp. ¹¹⁹
Coffee worker's lung	Coffee workers	Coffee bean dust	<i>Thermoactinomyces</i> spp. ¹²⁶
Humidifier lung	Office workers, others	Water reservoirs (contaminated ventilation systems)	<i>T. vulgaris</i> , <i>T. Candidus</i> , <i>M. faeni</i> ⁴
			<i>Bacillus cereus</i> ⁷⁰
			<i>Penicillium</i> spp. (fungi) ¹⁰
Fertilizer worker's lung	Fertilizer workers	Dirt	<i>Streptomyces albus</i> ⁶⁵
			endotoxin ⁴³
Detergent worker's lung	Detergent workers	Detergent beads, wood dust	<i>Bacillus subtilis</i> ^{45, 63}
	<i>Fungi</i>		
Wood worker's lung (maple bark stripper's lung, Sequoiosis, wood pulp worker's lung)	Maple bark strippers Lumber barkers Redwood workers Loggers	Moldy bark dust Moldy redwood dust	<i>Cryptostroma corticale</i> ³² <i>Aureobasidium pullulans</i> ²³ <i>Graphium</i> spp. <i>Alternaria tenuis</i> ⁶⁶ <i>Saccharomonospora viridis</i> ⁵⁰
Summer-type hypersensitivity pneumonitis	Occupants of Japanese wood houses	Wood Dust	<i>Cryptococcus neoformans</i> ⁸³
Dry rot disease	Old-house inhabitants (Europe)	Infected old wood	<i>Merulius lacrymans</i> ⁸⁵
Suberosis	Cork workers	Moldy cork dust	<i>Penicillium frequentans</i> ³
Malt worker's lung	Malt workers	Moldy malt and barley	<i>Aspergillus clavatus</i> ¹²
Paprika splitter's lung	Paprika splitters	Moldy paprika pods	<i>Mucor stolonifer</i> ⁶²
Wheat weevils disease	Flour workers	Infected wheat flour	<i>Sitophilus granarius</i> ¹¹
Cheese worker's lung	Cheese workers	Cheese mold	<i>Penicillium casei</i> ²⁴ <i>P. roqueforti</i> ¹⁷
Horseback rider's lung	Horsemen	Moldy barn straw	<i>Sporobolomyces</i> spp. ²²
Lichen picker's lung	Lichen pickers	Moldy lichen (<i>Cladonia alpestris</i>)	<i>Aspergillus</i> spp. <i>Rhizopus</i> spp. <i>Cladosporium</i> spp. <i>Penicillium</i> spp. ¹⁰⁴ <i>Aspergillus</i> spp. ⁶¹
Papermill worker's lung	Papermill workers	Moldy wood chips	
	<i>Animal Proteins</i>		
Avian protein diseases	Bird handlers	Parakeets	Avian proteins from serum, excreta or feather bloom ^{103, 129}
Bird fancier's disease		Pigeons	
Budgerigar-fancier's lung		Chickens	
Pigeon breeder's lung		Turkeys	
Poultry handler's lung		Ducks	
Furrier's lung	Furriers	Fox fur, other?	Animal hair protein ⁹⁷
Rodent handler's disease	Animal laboratory workers	Rats, gerbils	Urine, serum proteins ^{19, 71, 128}
Pituitary snuff-taker's lung	Snuff producers	Pituitary snuff	Porcine and bovine pituitary protein ⁵⁵

Lindersmith, L.A. et Al "Hypersensitivity Pneumonitis" in
Zenz, C *Occupational Medicine, Year Book Medical Publishing inc,*
chap 15, 228

- céphalée
- fièvre de 100° à 106°F après 4 à 8 heures d'exposition
- hémoptysie légère
- absence de sibilance sauf si l'asthme est concomittant

7.3.2 Examen clinique et laboratoire

A l'examen clinique, on observe :

- des râles basilaires plusieurs jours après le début
- il y a possibilité de cyanose

A l'examen de laboratoire on observe :

- leucocytose et éosinophilie

7.3.3 Pronostic

Si le sujet s'éloigne de l'allergène, dans 10 à 12 heures les symptômes diminuent graduellement sur une période de 2 semaines. Occasionnellement la dyspnée persiste plusieurs mois. Si les attaques sont fréquentes les symptômes augmentent : anorexie, perte de poids suivi d'un stage irréversible d'insuffisance pulmonaire et du ventricule droit ou coeur pulmonaire. Dans 1 à 15% des cas, la maladie est insidieuse avec tendance à développer plus tard des attaques aiguës typiques.

7.3.4 Immunologie et pathologie

Cette partie du sujet dépasse le besoin du présent document mais pour ceux qui sont intéressés les références traitent bien ces aspects.

7.3.5 Dépistage des alvéolites allergiques

Il n'y a pas présentement de tests médicaux bien évalués disponibles pour dépister les alvéolites allergiques. Possiblement, le dosage des anticorps spécifiques selon les expositions précises pourraient être envisagé, mais le coût-bénéfice serait la plus grande objection.

7.3.6 Information et prévention

L'information des travailleurs sur ces risques peut permettre un dépistage plus précoce et le diagnostic des travailleurs déjà atteints. Une infirmière et un médecin informés des symptômes ou des maladies pulmonaires chez les travailleurs exposés peuvent les diriger vers les experts aptes à compléter le diagnostic.

Les mesures préventives recommandées sont les suivantes :

- retrait de l'exposition à l'allergie pour les cas connus
- contrôle des poussières
- information des travailleurs

7.4 - Syndrome des poussières organiques

Le syndrome des poussières organiques porte aussi le nom de "mycotoxicose pulmonaire". Les symptômes similaires à l'influenza (grippe) apparaissent à la suite d'expositions à des concentrations élevées de produits d'agriculture et ce avec ou sans symptômes respiratoires et habituellement sans évidence clinique ou radiologique d'alvéolite allergique (parfois l'alvéolite clinique est présente).

7.4.1 Etiologie potentielle

Le syndrome des poussières organiques origine des poussières contenant des moisissures, des bactéries ou d'autres agents non identifiés. On observe 30 à 40% de prévalence chez les personnes exposées. Les poussières en cause sont :

- l'ensilage, le grain (tableau IV), les copaux de bois, etc. dont la caractéristique commune est d'être mois *produits détériorés et mois*
- la poussière de grain, de cochon, de volaille contaminée par des endotoxines.

7.4.2 Diagnostic différentiel

Ce syndrome se différencie de l'alvéolite allergique par les éléments suivants :

- 1) une proportion élevée des individus exposés deviennent symptomatiques
- 2) les niveaux de concentration environnementale sont toujours très élevés
- 3) aucun indice de maladie pulmonaire progressive en dépit d'expositions répétées
- 4) dans la plupart des cas les anticorps sériques ne sont pas détectés
- 5) le lavage alvéolaire pendant la phase aiguë révèle une prédominance de neutrophiles plutôt que de lymphocytes
- 6) la biopsie montre des inflammations mais sans granulome.

7.4.3 Dépistage et prévention

Aucun questionnaire ou test n'est valable jusqu'à présent bien que cela serait probablement utile. L'information aux travailleurs de l'existence de cette entité pathologique peut aider au dépistage. La prévention peut se faire par la protection personnelle et le contrôle de poussières.

7.5 - Bronchite chronique

Chez presque tous les groupes de travailleurs exposés à des poussières organiques on peut retrouver des bronchites chroniques. Cependant, comme pour les soudeurs, établir la relation avec le travail n'est pas toujours facile en particulier chez les fumeurs. Il existe par contre certaines études qui tendent à démontrer que pour des groupes de travailleurs précis tels que les mélangeurs de farine et les boulangers, la prévalence d'une maladie pulmonaire obstructive serait plus élevée comparée à des groupes de contrôle. Ces études sont basées sur la présence de symptômes sur des mesures des fonctions respiratoires.

Dépistage

Le dépistage de la bronchite est complexe vu que ces travailleurs peuvent présenter aussi de l'asthme. Les questionnaires existants ne couvrent pas nécessairement les deux pathologies bien que les tests de fonctions respiratoires s'appliquent bien aux deux. Le médecin responsable devra choisir les moyens de dépistage aux fins de ce qu'il veut rechercher. Dans le cas de la bronchite chronique le questionnaire ATS est valable. Le diagnostic précis se fera avec la connaissance précise du milieu de travail, de l'histoire du travailleur et des tests pulmonaires.

Tableau IV - Composition des poussières de grain

Grain de céréales (blé, orge, sarrasin, avoine, maïs et produits de désintégration)
Pesticides (tétraclorure de carbone, malathion, bromure de méthyl, phosphate d'aluminium, disulfure de carbone)
Débris de mammifère et débris aviaires (poids et excréments des rongeurs, pigeons)
Fungus et leurs métabolites (alfatoxine)
Pollens
Endotoxines bactériennes
Parties d'insectes
Mites
Silices

Maladies respiratoires

Asthme professionnel

Bibliographie

- * BERITIC-STAHULJAK, D., VALIC, F. et al., "Simultaneous Exposure to Airborne Flour Particles and Thermal Load as Cause of Respiratory Impairment", *Int. Arch. Occup. Environ. Health*, vol. 37, pp. 193-203, (1976).
- * BJÖRKSTÉN, F., BACKMAN, A. et al., "Immunoglobulin E specific to wheat and rye flour proteins", *Clinical Allergy*, vol. 7, pp. 473-483, (1977).
- * BLANDS, J., DIAMANT, B. et al., "Flour Allergy in Bakers", *Int. Archs Allergy appl. Immun.*, vol. 52, pp. 392-406, (1976).
- * BLOCK, G., TSE K.S. et al., "Baker's asthma" *Clinical Allergy*, vol. 14, pp. 177 - 185 (1984).
- * BOURBEAU, J., "Occupational Asthma : A Patient-Oriented Approach", *Canadian Journal of CME*, (November/December 1990).
- ** CHAN-YEUNG, M., "State of Art. Occupational Asthma.", *Am. Rev. Respir. Dis.*, vol. 133, pp. 686-703, (1988).
- * DSC HAUT-RICHELIEU, *Guide de surveillance médicale pour l'asthme professionnel*, avril 1991.
- * HENDRICK, D.J., DAVIES, R.J. et al., "Baker's Asthma", *Clinical Allergy*, vol. 6, pp. 241-250, (1976).
- * HERENG, M. P., DEMARTEAU, S. et al., "Evaluation du degré de sensibilisation aux allergènes professionnels et de l'incidence de l'asthme dans une population de boulangers d'une industrie de la région liégeoise", *Cahiers de médecine du travail*, vol. XXV, no. 4, (1989).
- * LEHRER, S.B., "Bean Hypersensitivity in Coffee Workers' Asthma : A Clinical and Immunological Appraisal" *Allergy Proceedings*, vol. 11, no. 2, pp. 65-66, (1990).
- * LEHRER, S.B., "Hypersensitivity Reactions in Seafood Workers", *Allergy Proceedings*, vol. 11, no. 2, pp. 67-68, (1990).

- * MALO, J.L., "L'asthme professionnel - Rapport du comité spécial de la Société de thoracologie du Canada", *Le Clinicien*, (mars 1988).
- * MC NUTT, G.M., "Screening for Occupational Asthma : A Word of Caution", *Journal of Occupational Medicine*, vol. 33 no. 1, pp. 19-22, (1991).
- * MUSK, A.W., VENABLES, K.M., "Respiratory Symptoms, Lung Function, and Sensitisation to Flour in a British Bakery", *British Journal of Industrial Medicine*, vol. 46, pp. 636-642, (1989).
- * "Occupational Disease Surveillance : Occupational Asthma", *Morbidity and Mortality Weekly Report*, vol. 39, no. 7, pp. 119-123, (23 fév. 1990).
- * O'NEIL, C., "Occupational Respiratory Diseases Resulting from Exposure to Eggs, Honey, Spices and Mushrooms", *Allergy Proceedings*, vol. 11, no. 2, pp. 69-70, (1990).
- * PRICHARD, M.G., RYAN, G. et al., "Wheat flour sensitisation and airways disease in urban bakers", *British Journal Industrial Medicine*, vol. 41, pp. 450-454, (1988).
- * TSE, K.S., "Grain Dust Asthma" *Allergy proceedings*, vol. 11, no. 2, pp. 61-62, (1990).
- * ZUSKIN, E., KANCELJAK, B. et al., "Acute Effects of Herbal Tea Dust Extracts on Lung Function", *Chest*, vol. 96/6, (december 1989).

* Articles joints

** Le texte est inclus dans le *Guide de surveillance médicale pour l'asthme professionnel* (ci-joint).

Simultaneous Exposure to Airborne Flour Particles and Thermal Load as Cause of Respiratory Impairment

DUNJA BERITIĆ-STAHULJAK, F. VALIĆ, MIRA CIGULA,
and D. BUTKOVIĆ

Andrija Štampar School of Public Health, Zagreb University,
Rockefellerova 4, Zagreb, Yugoslavia

Summary. In order to estimate whether only simultaneous exposure to both airborne flour particles and unfavorable thermal environment alone cause the development of nonspecific respiratory disease or whether sole exposure to flour aerosols is likely to cause impairment of the respiratory system, a group of 80 millers and 130 bakers, all nonsmokers, were examined. Both millers and bakers were exposed to approximately the same concentration of airborne flour particles but the latter worked under considerable thermal load. It was found that between millers and bakers the difference in the prevalence of respiratory symptoms was not statistically significant. Although the differences between the mean measured and the mean predicted ventilatory function parameters (FVC, FEV₁, PEF, MEF 50%, MEF 75%) were significant both in millers and bakers, they did not differ significantly between these two groups. This finding suggests that exposure to flour dust may cause the development of chronic nonspecific respiratory disease and a reduction of ventilatory lung capacity, irrespective of simultaneous heat load.

Key words: Flour particles - Thermal load - Respiratory impairment.

INTRODUCTION

Ramazzini, as early as the 18th century, described occupational asthma caused by flour particles [29]. A number of publications can be found later in the literature describing allergic effects of flour in the form of bronchial asthma and rhinitis in bakers and millers [1, 6, 8, 10-16, 19-22, 27, 32, 33]. In a previous publication we showed that the long-term exposure to flour particles brings about respiratory symptoms and impairment of ventilatory lung capacity in bakers [34]. We studied the relationship between hypersensitivity to flour and the prevalence of chronic bronchitis in bakers [4]. Examining the role of bacterial and fungal flora in the development of chronic bronchitis in bakers we found no significant difference in the frequency of pathogenic agents in bakers with and without chronic bronchitis.

This observation together with the finding that among the bakers, in whose expectorations predominantly pathogenic agents were isolated, there were many without chronic bronchitis, has given ground to the assumption that in bakers' chronic bronchitis it is not infection that plays the most important role [5]. Examining a possible direct pharmacodynamic effect of flour particles on the respiratory system we showed the presence of agents that contract smooth muscles [35].

All previous studies of the influence of flour particles on the ventilatory lung capacity and the development of respiratory symptoms have been conducted in bakers. Bakers, as a rule, are exposed not only to flour particles but also, simultaneously, to unfavorable thermal conditions. It is, therefore, impossible to rule out the additional influence of thermal factors in the development of nonspecific lung disease in bakers. In order to assess quantitatively separate contributions of exposure to flour dust and unfavorable thermal environment, we studied two population groups exposed to similar airborne concentrations of flour dust but working under significantly different thermal condition: a group of millers exposed to flour particles under normal thermal conditions and a group of bakers simultaneously exposed to flour particles and to a considerable thermal load.

POPULATION AND METHODS

Sample. 163 millers and 322 bakers were examined. Data on 80 millers and 130 bakers (nonsmokers) were processed in detail in order to exclude the additional effect of smoking on the ventilatory function and the development of respiratory symptoms. The age distribution of the latter was very similar, the mean age of the millers being 37 years, and of the bakers 37.5 years. They differed little in their average length of service (millers: 16.1 years; bakers: 17.5 years).

Evaluation of Work Environment. Hexhlet two-stage dust samplers were used for the sampling of total and respirable particles [38]. Air temperature, humidity, air motion, and radiant heat were measured with standard field instruments. Corrected effective temperature (CET) [2] was read and wet bulb globe temperature (WBGT) [38] and heat stress index by Belding and Hatch (HSI) [3] were calculated.

Ventilatory Function. Pulmonor spirometers¹ were used for the measurement of the forced vital capacity (FVC) and the forced expiratory volume in the first second (FEV₁). Five measurements were taken in each subject and the mean of the two highest

values
calcula
Communi
using W
calcula
facture
changes
curves
the max
75%) of
curves
by Pete
lated u

Respirat
standar

RESULTS

Assessm

The res
the wor
sented
in seve
mg/m³;
centrat
and the
and the
The gec
mg/m³,
1.09 ar
lers ar

Evaluat

The res
and the
sented
as cor
and as
lation
pressi
where 1

¹Jones Medical Instrument Co., 200 Windsor Bldg., Oakbrook, Ill., USA.

²Airmet
³Emmerson

values was taken as the result. Predicted normal values were calculated using the tables of the European Coal and Steel Community [7]. The peak expiratory flow (PEF) was measured using Wright's instrument. The predicted normal values were calculated using the prediction equation provided by the manufacturer [31]. For the detection of possible obstructive changes in small airways the maximum expiratory flow-volume curves were recorded in a smaller group of workers on which the maximum expiratory flow at 50% (MEF 50%) and at 75% (MEF 75%) of the control vital capacity were read. The flow-volume curves were recorded by means of the flow-volume spirometer by Peters et al. [28]. The predicted normal values were calculated using the equations by Cherniak and Raber [9].

Respiratory Symptoms. Respiratory symptoms were recorded using the standard British Medical Research Council Questionnaire [24].

RESULTS

Assessment of Dust Exposure

The results of the determination of airborne flour particles in the working environments of the mill and the bakery are presented in Table 1 as cumulative frequencies of concentrations in seven concentration classes (total particles: 0.50 - 3.99 mg/m³; respirable particles: 0.50 - 2.24 mg/m³). The mean concentrations of total particles were 2.02 mg/m³ and 2.25 mg/m³, and the mean concentrations of respirable particles in the mill and the bakery were 0.88 mg/m³ and 1.20 mg/m³, respectively. The geometric means for total particles were 2.39 and 1.85 mg/m³, and for respirable particles in the mill and the bakery 1.09 and 1.13 mg/m³, respectively. The exposure levels of millers and bakers were found to be similar.

Evaluation of Thermal Exposure

The results of the measurements of thermal factors in the mill and the bakery in two different seasons of the year are presented in Table 2. The level of thermal exposure is expressed as corrected effective temperature, wet bulb globe temperature and as heat stress index by Belding and Hatch. Heat accumulation, expressed in kcal/h, was calculated using the expression [18]: $A = M + 6.6(t_r - 35) + 0.6v^{0.6}(t_a - 35) - 1.2v^{0.6}(42 - p_a)$, where M = energy expenditure (kcal/h); t_r = globe temperature (°C);

²Airmed Ltd., Edinburgh, Scotland.

³Emmerson Comp., Ltd., Cambridge, Ma., USA.

Table 1. Concentrations of Airborne particles of mill and bakery

Particles of all sizes					Respirable fraction				
Concentration (mg/m ³)	Frequency		Cumulative frequency (%)		Concentration (mg/m ³)	Frequency		Cumulative frequency (%)	
	Mill	Bakery	Mill	Bakery		Mill	Bakery	Mill	Bakery
0.50 - 0.99	2	11	7.14	12.08	0.50 - 0.74	12	4	42.85	19.04
1.00 - 1.49	2	11	14.28	24.17	0.75 - 0.99	1	4	46.42	38.09
1.50 - 1.99	8	24	42.85	50.55	1.00 - 1.24	3	2	57.14	47.61
2.00 - 2.49	1	15	46.42	67.03	1.25 - 1.49	6	6	78.57	76.19
2.50 - 2.99	6	18	67.85	86.81	1.50 - 1.74	4	4	92.85	95.23
3.00 - 3.49	3	5	78.57	92.31	1.75 - 1.99	0	0	92.85	95.23
3.50 - 3.99	6	7	100.00	100.00	2.00 - 2.24	2	1	100.00	100.00
Total dust					Respirable fraction				
			Mill	Bakery				Mill	Bakery
Arithmetic mean (mg/m ³)			2.02	2.25				0.88	1.20
Geometric mean (mg/m ³)			2.39	1.85				1.09	1.13

v = air
vial pr
calcula
bakers
their c
ary act
ing the
were di
much be
between
the fou
The
wet bul
to be c
in the
and the
values
thresho
Health
Occupat

Bakery

Mill

Warm seas

Bakery

Mill

Cool seas

Plant

Table 2

Table 2. Thermal environment in mill and bakery

Plant	Operation	Weighted average work load (kcal/h)	Outdoor air temperature (°C)	CET (°C)	WBGT (°C)	Heat accumulation (kcal/h)	HSI
<i>Cool season</i>							
Mill	Milling and sieving	147	14	16	14.1	-302.2	-7.5
	Packing	157		12	11.2	-379.9	-19.5
Bakery	Dough preparation	172	14	22.5	21.4	-143.1	38.1
	Bread baking	165		24.5	22.8	-654	70.4
<i>Warm season</i>							
Mill	Milling and sieving	147	23	22.5	21.6	-190.2	22.7
	Packing	157		21	20.7	-253.9	12.3
Bakery	Dough preparation	172	23	25.5	24.8	-94.4	56.3
	Bread baking	165		27.8	26.6	-17.2	91.6

v = air motion (m/min); t_a = air temperature (°C); and P_a = partial pressure of water vapor (mm Hg). The mean work load was calculated by weighing the energy expenditures in millers and bakers estimated by Mavor and Boras [23] after having analyzed their time distribution between the main work activity, auxiliary activities, and rest. Although the energy expenditures during the main activities of the four groups of the examinees were different, the weighted average work load did not differ much because of considerably different distributions of time between the main activity, auxiliary activities, and rest in the four groups of subjects.

The time-weighted values of corrected effective temperature, wet bulb globe temperature and the heat stress index were found to be considerably higher in the bakery than in the mill, both in the cool early spring season (mean outdoor temperature 14°C) and the warm summer season (mean outdoor temperature 23°C). The values of WBGT both in the bakery and the mill, were below the threshold WBGT values proposed by the Occupational Safety and Health Standards Advisory Committee on Heat Stress of the U.S. Occupational Safety and Health Administration in 1974 [23,30].

Table 3. Prevalence of respiratory symptoms in millers and bakers

	Chronic bronchitis	Dyspnea	Wheezing	Nasal catarrh	Bronchial asthma
Millers	15 (18.8%)	22 (27.5%)	15 (18.8%)	27 (33.8%)	2 (2.5%)
Bakers	30 (23.0%)	54 (41.5%)	29 (22.3%)	39 (30.0%)	4 (3.1%)
χ^2 -test	1.34; P>0.05	16.87; P<0.01	1.05; P>0.05	0; P>0.05	0.03; P>0.05
Control group ^a	6.0%	11.0%	4.9%	14.2%	0%

^a Cited after [35].

Table 4

Mean measured and predicted values of FVC, FEV₁, and PEF in millers and bakers, and significance of their difference

	FVC			FEV ₁			PEF		
	Measured	Pre- dicted	P	Measured	Pre- dicted	P	Measured	Pre- dicted	P
Millers N = 80	4276	5072	<0.01	3422	3897	<0.01	510	609	<0.01
Bakers N = 130	4232	4808	<0.01	3403	3704	<0.01	522	606	<0.01

just as the time-weighted values of CET were below the upper limits proposed by the WHO Scientific Group on Health Factors Involved in Working Under Condition of Heat Stress in 1969 [25]. It is obvious, however, that the heat exposure of bakers was much higher than that of millers. In fact, the high values of all the three thermal indices in the bakery compared with the low values in the mill show that the bakers were exposed to a considerable thermal burden, particularly in the warm season of the year, while the millers worked under comfortable thermal conditions all the year round.

Respiratory Symptoms and Ventilatory Function

The prevalence of respiratory symptoms in millers and bakers is presented in Table 3. The prevalence of all respiratory symptoms in the workers exposed to flour dust was considerably higher than that found in our control group of nonsmokers of similar age distribution studied a few years ago [35], but

Table
Mean m
bakers

Miller:
N = 47

Bakers
N = 37

Table
Mean d
in mil

Miller

Bakers

P

there
pirat
for d
baker

Th

predi
value
to be
(P<0.

Th
nific
group
recor
volum
study

In
on th
measu
meter
baker
betwa
venti
these

Table 5.

Mean measured and predicted values of MEF 50% and MEF 75% in millers and bakers, and significance of their difference

	MEF 50%			MEF 75%		
	Measured	Predicted	P	Measured	Predicted	P
Millers N = 47	5.1	5.6	<0.05	2.0	2.8	<0.05
Bakers N = 37	5.0	5.6	<0.05	2.3	2.9	<0.05

Table 6.

Mean differences of measured and predicted values of spirometric parameters in millers and bakers and significance of differences between these means

	FVC	FEV ₁	PEF	MEF 50%	MEF 75
Millers	-781.7	-475.4	-96.5	-0.51	-0.68
Bakers	-555.8	-254.3	-82.4	-0.72	-0.97
P	> 0.05	> 0.01	> 0.05	>0.05	>0.05

there was no significant difference in the prevalence of respiratory symptoms between millers and bakers ($P>0.05$) except for dyspnea, the prevalence of which was found to be higher in bakers ($P<0.01$).

The mean values of FVC, FEV₁, and PEF, as well as the mean predicted normal values are shown in Table 4. The mean measured values of all three ventilatory function parameters were found to be significantly lower than the expected normal values ($P<0.01$) both in millers and in bakers.

The mean measured values of MEF 50% and MEF 75% were significantly lower than the expected values ($P<0.05$) in both groups of the examinees (Table 5). The flow-volume curves were recorded in 47 millers and 37 bakers only, because the flow-volume spirometers were not available at the beginning of the study.

In order to compare the magnitude of the chronic dust effect on the two groups of examinees the mean differences between the measured and the expected values of ventilatory function parameters in millers were compared with the same differences in bakers (Table 6). In both millers and bakers the differences between the mean measured and the mean expected values of all ventilatory function parameters were considerable, but between these two groups they did not differ significantly ($P>0.05$).

DISCUSSION

In a previous publication, we showed that a long-term exposure to flour particles is likely to bring about a higher prevalence of respiratory symptoms and a reduction of ventilatory lung capacity in bakers [35]. During that study attention was not paid to another occupational risk of bakers, namely, to the unfavorable thermal conditions which might also contribute to the impairment of the respiratory system. In the present study, in order to assess whether sole exposure to flour particles causes impairment of the respiratory system, we compared bakers, exposed simultaneously to airborne flour particles and unfavorable thermal environment and millers exposed to flour particles only.

Estimating the thermal environment of millers and bakers, significant differences were found in their heat load (Table 2). The bakers were exposed to much higher thermal exposure than the millers whose thermal environment was found to be pleasant both in the cool and warm season of the year. Millers and bakers with an approximately equal level of dust exposure were chosen for the study in order to compare two population samples exposed to practically equal airborne dust concentrations but differing in their thermal burden. Only nonsmokers were chosen in order to eliminate smoking, a factor which undoubtedly contributes to the development of chronic respiratory symptoms. The analysis of chronic nonspecific respiratory symptoms has shown that the prevalence of chronic bronchitis, dyspnea, wheezing, nasal catarrh, and bronchial asthma was significantly higher in both millers and bakers as compared with the control group, but that there was no significant difference between bakers and millers, except for dyspnea which was found to be significantly higher in bakers (Table 3). The analysis of ventilatory function has shown that the measured values of all ventilatory capacity parameters of both millers and bakers were lower than the expected normal values calculated on the basis of their height and age (Tables 4 and 5).

In order to answer the main question whether the exposure to airborne flour particles, without simultaneous heat load, causes changes in pulmonary ventilation, the effects found in millers and bakers were compared. As the height and age distributions of millers and bakers were not identical, it was considered unjustifiable to compare directly the measured values of ventilatory capacity in the two groups. The expected normal values of all the ventilatory function parameters were calculated for each examinee, as well as the difference between the expected and the measured values. The means of these differences were calculated separately for bakers and millers and the difference of these means was tested by the t-test for unpaired variables. The results presented in Table 6 show that there was

no difference between the dust measured thermal effect of

To our comparison authors

It is more than the high than in than 77% service age of 4

years. A millers lower value ably high on height

Our results the development a reduction ultaneous

REFERENCE

1. Baagø
2. Bedford Counc.
3. Beldi resul
4. Berit flour (1971)
5. Berit in the med. j.
6. Castb Acta
7. CECA: (1967)
8. Cenac forna
9. Chern using
10. Colme fluen of 32

no difference between bakers and millers as to the magnitude of the dust effects on any of the ventilatory capacity parameters measured. The simultaneous exposure of bakers to unfavorable thermal environment did not contribute significantly to the effect of flour dust exposure on the respiratory system.

To our knowledge, only one paper has been published so far, comparing spirometric findings in bakers and millers [26]. The authors have found greater reductions of FEV₁ and FVC in bakers. It is most likely that their findings are to be attributed to the higher age and a much longer length of service in the bakers than in the millers examined. Among their bakers there were more than 77% above the age of 40 and more than 71% with a length of service of over 20 years, compared with 44% of millers above the age of 40 and only 19.4% with the length of service of over 20 years. As they were comparing the means of FEV₁ and FVC between millers and bakers, without adjustment for age and height, the lower values in the bakers were most likely due to a considerably higher age and length of service (they did not give data on height distribution).

Our results suggest that exposure to flour dust may cause the development of nonspecific chronic respiratory disease and a reduction of ventilatory lung capacity irrespective of simultaneous heat load.

REFERENCES

1. Baagoe, K.H.: Mehlidiosynkrasie. Klin.Wschr. 1, 792 (1933)
2. Bedford, T.: Environmental warmth and its measurement. Medical Research Council War Memo, No.17. London: HMSO 1946
3. Belding, H.S., Hatch, T.F.: Index for evaluating heat stress in terms of resulting physiological strains. Heat.Pip.Air Condit. 27, 129 (1955)
4. Beritić, D., Valić, F.: On the relationship between hypersensitivity to flour and chronic bronchitis in bakers [in Croatian]. Lij.vjes. 93, 991 (1971)
5. Beritić, D., Valić, F., Zagar, Z.: Role of bacterial and fungal flora in the development of chronic bronchitis in bakers [in Croatian]. Acta med.jugosl. 26, 19 (1972)
6. Castberg, T., Sorensen, C.M.: Allergic examinations of bakers and millers. Acta Allerg. 1, 283 (1948)
7. CECA: Tables de références pour les examens spiromographiques, Luxembourg (1967)
8. Cenacchi, G.C., Rosa, L., Bergami, G.: Indagine sulle allergopatie dei fornai. Folia med. 42, 345 (1959)
9. Cherniack, R., Raber, M.B.: Normal standards for ventilatory function using an automated wedge spirometer. Amer.Rev.resp.Dis. 106, 38 (1972)
10. Colmes, A., Guild, T.B., Rackemann, F.M.: Studies in sensitization; influence of occupation on sensitization in man as determined in study of 32 bakers. J.Allergy 6, 358 (1935)

11. Danilović, V., Karajović, D., Ljaljević, M., Popović, D., Spužić, I.: Examen de l'allergie chez les boulangers et les meuniers. Acta med. jugosl. 13, 294 (1959)
12. Diedrich, W., Lübbers, P.: Das Mehlasthma als Berufskrankheit. Z.Arbeitsmed.Arbeitsschutz 5, 189 (1955)
13. Dishoek, V., Roux, D.J.: Sensitization to flour and respiratory illnesses among flour workers. J.Hyg.(Lond.) 34, 674 (1934)
14. Epstein, U.: Cited in: P. Bonevie, Occupational allergy. Leiden: Stenfert 1958
15. Gadborg, S.: Allergy to flour. Doctoral Thesis, Copenhagen (1956). Cited in: P. Bonnevie, Occupational allergy. Leiden: Stenfert 1958
16. Granati, A., Capone, C.: Studio sulle condizioni ambientali e sulla patologia professionale nei laboratori artigiani della fabbricazione del pane. Folia med. 42, 948 (1959)
17. Health factors involved in working under conditions of heat stress. Techn.Rep.Ser., No.412. Geneva: W.H.O. 1969
18. Hertig, B.A.: Thermal standards and measurement techniques. In: The industrial environment evaluation and control, p.413. Washington N.I.O.S.H. 1973
19. Herxheimer, H.: Die Entwicklung von Mehlempfindlichkeit der Haut bei Bäckerlehrlingen und Bäckern. Klin.Wschr. 45, 481 (1967)
20. Hlavaček, H.A.E.: Allergic symptoms on the mucous membrane of the respiratory tract of bakers and millers. Acta oto-laryng.(Stockh.) 26, 358 (1938)
21. Klunker, W.: Zur Frage der Aetiologie und Pathogenese des sogenannten Bäcker- und Müllerasthmas. Schweiz.med.Wschr. 87, 714 (1957)
22. Linko, E.: Allergic rhinitis and bronchial asthma in bakers. Ann.Med. intern.Fenn. 34, 98 (1947)
23. Maver, H., Boras, E.: A contribution to the knowledge of energy expenditures in bakers [in Croatian]. Proceedings of the Fourth Congress on Preventive Medicine, Sarajevo, Yugoslavia (1961)
24. Medical Research Council Committee on the Aetiology of Chronic Bronchitis: Definition and classification of chronic bronchitis for clinical and epidemiological purposes. Lancet II 1965, 775
25. National Institute of Occupational Safety and Health: Criteria for a recommended standard. Occupational exposure to hot environment. HSM - 1972 - 10269, Cincinnati (1972)
26. Odavić, M., Cvetanov, V.I.: Incidence of the allergic manifestations and phenomena of pulmonary spastic syndrome in the workers exposed to flour and floury dust. Allergie u. Asthma 15, 364 (1969)
27. Pestalozzi, C., Schnyder, U.W.: Zur Frage der Bäckerrhinitis und des Bäckerasthmas. Schweiz.med.Wschr. 85, 496 (1955)
28. Peters, J.M., Mead, J., Van Ganse, W.F.: A simple flow-volume device for measuring ventilatory function in the field. Amer.Rev.resp.Dis. 99, 617 (1969)
29. Ramazzini, B.: Le malattie dei lavoratori (de morbis artificum diatriba). Torino: Minerva medica 1933
30. Ramsey, J.D.: A heat stress standard - How do we face up to it? Presented to American Society of Safety Engineers Professional Development Conference, Pittsburgh, PA. (1974)

31. Regre...
- Airmex
32. Salen...
- ter A...
- piell
33. Spužić...
- Nikol...
- Petro...
34. Spužić...
- ration...
- niers
35. Valić...
- Lij.v...
36. Valić...
- teris...
- (1972)
37. Valle...
- forna...
38. Wrig...
- Med.
39. Yaglo...
- ing co

Received

31. Regression formula for PEF values expected in normal men. Edinburgh: Airmed Ltd.
32. Salen, E.B., Juhlin-Dannfelt, C.: Über das Vorkommen von soggl. latenter Allergie. Gleichzeitig einige Gesichtspunkte über gewisse prinzipiell bedeutungsvolle Allergieprobleme. Acta med.scand. 80, 505 (1965)
33. Spužić, B., Bojanić, B., Milijić, B., Perišić, S., Ljaljević, J., Nikolić, V.: Allergy in workers employed in steam bakery and mill in Petrovac na Mlavi [in Serbian]. Zavod zdrav.zašt.SRS 1, 21 (1963)
34. Spužić, V., Bojanić, M., Spužić, I.V.: La role de la farine dans l'apparitions des manifestations allergiques chez les boulangers et les meuniers en Yougoslavie. Acta allerg.(Kbh.) 23, 69 (1968)
35. Valić, F., Beritić, D.: Chronic bronchitis in bakers [in Croatian]. Lij.vjes. 93, 739 (1971)
36. Valić, F., Tudić, G., Beritić, D., Gjuriš, V.: Pharmacodynamic characteristics of flour particles [in Croatian]. Acta med.jugosl. 26, 29 (1972)
37. Vallerani, G., Bonino, R.: Rilievi sulle allergopatie respiratorie nei fornai. Minerva med. 54, 3069 (1963)
38. Wright, B.M.: A size-selecting sampler for airborne dust. Brit.J.industr. Med. 11, 284 (1954)
39. Yaglou, G.P., Minard, D.: Control of heat casualties at military training centres. Arch.Industr.Hlth 16, 302 (1957)

Received December 18, 1975 / Accepted February 13, 1976

*Wheat
Rye*

Immunoglobulin E specific to wheat and rye flour proteins

E. BJÖRKSTÉN, A. BACKMAN, K. A. J. JÄRVINEN, H. LEHTI,
E. SAVILAINEN, P. SYVÄNEN and T. KÄRKKÄINEN

Hospital for Allergic Diseases and Children's Hospital,
Helsinki University Central Hospital, Helsinki, Finland

Summary

We have used the radioallergosorbent test (RAST) to determine IgE antibodies specific to wheat flour proteins in the sera of seven groups of patients. In some cases rye-specific IgE was also determined. Wheat and rye RAST scores showed a good correlation, presumably due to cross-reactions. Among bakers with asthma, positive scores, 0-5/3, occurred with a prevalence of 43%, and among children with eczema, scores in the range 0-5/4 were found with a prevalence of 54%. A score of 0-5 was a marginal value which was also occasionally encountered with sera from patient groups with no history of immediate hypersensitivity to wheat or rye. These groups included adults and children with allergic rhinitis and asthma, children from the general population and children with coeliac disease. The RAST appeared useful in the diagnosis of allergy to inhaled flour dust among bakers. Among children with eczema, positive wheat and rye RAST results were a common finding, which only occasionally could be linked to strong and unequivocal reactions to the foods in question. Both in bakers and children with eczema, wheat and rye RAST results showed good agreement with intracutaneous skin test results.

Introduction

Wheat and rye flour dusts cause asthma and rhinitis in bakers (Hendrick, Davies & Pepys, 1976; Nakazawa *et al.*, 1976; Wilbur & Ward, 1976), and immunoglobulin E (IgE) specific to flour proteins can frequently be found in the sera of those affected (Blands *et al.*, 1976). In several studies manifestations of immediate hypersensitivity have been found in some 20% of the workers exposed (Linko, 1947; Borchert, 1972; Herzheimer, 1973).

Overt allergy to cereal grains ingested as foods occurs in children and young adults (Heiner, Goldstein & Rose, 1970; Hoffman & Haddad, 1974; Hoffman, 1975). Also these patients usually have circulating IgE specific to cereal grain proteins. In children with eczema, cereal-specific IgE can frequently be found even in the absence of overt symptoms to the cereals in question (Hoffman, 1975; Hoffman *et al.*, 1975).

To obtain further information on the occurrence of wheat- and rye-specific IgE, Correspondence: Dr E. Björkstén, Hospital for Allergic Diseases, SF-00250 Helsinki 25, Finland.

we have sought these antibodies in sera from asthmatic bakers, eczematous children and several other groups of allergic and non-allergic patients. In relevant groups, the results have been compared with skin and challenge test results, and with data from patients' histories. In particular, we have tried to firmly establish the groups in which cereal-specific IgE is to be found, and the clinical significance of this finding.

Patients and methods

Patients

We studied seven groups of patients.

Group (a) included twenty-one bakers with asthma, twelve women and nine men, with a mean age of 43.2 years (Table 1). Most patients had also rhinitis and two had eczema. They had worked in bakeries for 0.5–14 years, mean 4.7 years. Sixteen had a history suggesting allergy to wheat or rye flour dust. These allergies could not be distinguished by history. Only patients P.P. and R.E. had asthma before entering the trade.

Group (b) included thirty-nine adults, twenty-five women and fourteen men, with a mean age of 40.8 years, range 15–68 years. Most patients had asthma, and many suffered from immediate hypersensitivity as suggested by history, serum total IgE levels, blood eosinophil counts and secretory eosinophils. In a few cases the asthma could be classified as intrinsic. No patient had a history of allergy to wheat or rye, and no-one was a baker.

Group (c) included forty-one children, twenty girls and twenty-one boys, with a mean age of 3.1 years (Table 3). All had eczema presumably related to immediate hypersensitivity. In addition, eleven had asthma, three rhinitis and one spastic bronchitis. Seven patients had a history suggesting sensitivity to foods containing wheat or rye.

Group (d) included thirty-four children, eighteen girls and sixteen boys, with a mean age of 3.3 years. The age distribution of the group was matched to that of group (c). The patients were being treated for various surgical, urological and neurological conditions. The group was assumed to represent the general population as far as immediate hypersensitivity was concerned.

Group (e) included twenty-four children, nine girls and fifteen boys, with a mean age of 8.5 years, range 6–11 years. Most children had rhinitis and some asthma. No-one had present serious eczema. In all patients symptoms were due to immediate hypersensitivity as suggested by history, serum total IgE, blood eosinophil counts and secretory eosinophils. No patient had a history of allergy to wheat or rye.

Group (f) included ten children, seven girls and three boys, with a mean age of 7.0 years, range 0.5–16.5 years. All had biopsy-verified coeliac disease. Serum samples were taken prior to withdrawal of gluten from the diet.

Group (g) included 136 patients, all of whom had wheat- or rye-specific IgE, or both, in their serum. The group was studied to elucidate the correlation between wheat- and rye-specific IgE concentrations. Some of the patients were also included in group (a) or (c).

Allergy tests

For intracutaneous skin tests 1:100 wheat flour and rye flour extracts in Coca's solution were used. A skin reaction was regarded as positive when the area of the

weal caused by the allergen was larger than that caused by Coca's solution alone, and at least half as large as that caused by 100 mg/l histamine dihydrochloride in Coca's solution.

In nasal challenge tests bakers sniffed wheat or rye flour. If nasal, eye or bronchial symptoms developed within 15 min, the test result was regarded as positive. Test conditions were not ideal, since the bakers continued working and many had symptoms at the start of the test.

In preparation for an oral challenge, children were kept on a wheat- or rye-free diet for 3 days. They were then given 10 g wheat or rye flour, respectively, in the form of a boiled cereal. The test result was considered positive if skin, respiratory, gastric or generalized symptoms developed within 24 hr. The test was not repeated.

Serum total IgE was determined using the Phadebas IgE test kit (Pharmacia Diagnostics). Results are given in μ /ml (Rowe, Grab & Anderson, 1973).

Determination of wheat- and rye-specific IgE

Specific IgE was determined using the radioallergosorbent test (RAST) (Johansson, Bennich & Herg, 1971).

To obtain antigens, flours were extracted with an acid solvent (to dissolve gliadins) and with a neutral solvent (to dissolve albumins and globulins). Wheat flour was suspended in the ratio of 1 g per 3 ml and rye flour in the ratio of 1 g per 4 ml of 50 mmol/l sodium acetate buffer, pH 3.8. The suspensions were mixed for 45 min at room temperature, centrifuged, and separated into supernatant and precipitate, which were both saved. The precipitates were homogenized and resuspended using the original volume of 10 mmol/l sodium phosphate buffer, pH 7.0, containing 430 mmol/l sodium chloride. Suspensions were again mixed, centrifuged and separated, and the supernatant was saved. Both extraction solvents contained 4 g/l phenol as preservative. All extracts were concentrated ten-fold using ultrafiltration through a Diaflo[®] UM-2 membrane (Amicon Corp.).

The proteins from fresh flour extracts were coupled to cyanogen bromide-activated paper discs (Ceska & Lundkvist, 1972). To prepare wheat flour discs, both acid and neutral wheat extracts were added in equal volume to the same coupling solution. The volumes 7.5, 25 and 75 μ l of each extract per disc were tried in experimental runs, and the volume giving the highest count rate in a subsequent determination of specific IgE, in a suitable test serum, was chosen for the preparation of routine assay discs. Volumes chosen varied from lot to lot. Rye flour discs were prepared similarly. Reagents other than discs needed for the specific IgE determination were obtained from Phadebas RAST kits (Pharmacia Diagnostics).

Assay, calibration and result reporting procedures were mainly as described by the manufacturer for Phadebas RAST kits. This includes the use of a semi-quantitative, 0-4 RAST score based on the use of a reference serum dilution series and reference allergen discs. We modified the system to include the score 0.5, with which we describe the specific IgE concentration in a sample giving a count rate at least twice the background, but less than that required for RAST score 1 (approximately thrice the background). Our 'background' is the lowest count rate given by a patient sample in a RAST series of at least fifty assays. For the present we will consider a RAST score of 0.5 or higher as positive, i.e. as an indication of the presence of specific IgE.

Table 1. Patient group (a): twenty-one bakers with asthma

Patient	Sex	Age (years)	Diagnoses*	Blood eosinophils ($\times 10^9/l$)	Serum total IgE (u/ml)	History	Wheat flour		Rye flour	
							Specific IgE (RAST score)	Nasal challenge	Specific IgE (RAST score)	Nasal challenge
							Skin test		Skin test	
S.M.	M	24	A, R	200	730	+	+	0.5	+	0
L.H.	M	24	A, R	150	50	+	+	0.5	+	0
K.K.	F	24	A, R	350	70	+	+	0.5	+	0
M.H.	F	23	A, E, R	600	350	+	+	0	+	0
K.L.	M	23	A, E, R	250	1400	+	+	0	+	0
H.G.	M	20	A, R	150	380	+	+	0	+	0
P.J.	M	20	A, R	440	130	+	+	3	+	0
S.K.	F	20	A, R	130	20	+	+	1	+	0
E.A.	F	18	A, R	130	20	+	+	0	+	0
L.K.	F	18	A	440	560	+	+	0	+	0
T.E.	F	14	A, R	900	40	+	+	0	+	0
A.S.	F	14	A, R	70	390	+	+	0	+	0
A.K.	F	14	A, E, R	420	1300	+	+	0	+	0
K.I.	F	14	A, R	150	20	+	+	2	+	0
O.S.	M	13	A, R	70	10	+	+	0	+	0
P.P.	M	13	A, R	480	450	+	+	0.5	+	0
E.H.	F	12	A	150	30	+	+	2	+	0
R.E.	F	11	A, R	150	30	+	+	0	+	0
T.T.	F	11	A, R	110	190	+	+	0	+	0
E.P.	M	9	A, R	110	720	+	+	0	+	0
E.P.	F	9	A, R	40	40	+	+	0.5	+	0
Means				273	354			0		0
Logarithmic means				200	159					

* A, Asthma; B, bronchitis; E, eczema; R, rhinitis.

Results

Adults

We found wheat-specific IgE in the RAST score range 0.5-3 in the sera of nine (43%) out of twenty-one asthmatic bakers in patients group (a) (Table 1). In five cases the wheat-specific IgE was accompanied by rye-specific IgE. Rye-specific IgE did not occur alone. When history, skin test, nasal challenge test and specific IgE results were compared, skin test results were found to agree best with other data (Table 2). When two types of data were considered at a time, the best agreement was found between skin test and specific IgE results. These agreed in 85% of the cases—that is, both results were negative or both were positive 85% of the time.

The results for the bakers may be compared with those for other adult patients, mainly with asthma, in patient group (b). Wheat-specific IgE was found in only one (3%) of the sera from thirty-nine patients. In the positive case the RAST score was 0.5. No rye-specific IgE was found in any of the nineteen sera examined. Intracutaneous skin tests were performed in nineteen patients with one (5%) positive result. The positive patient was not the one with wheat-specific IgE.

Children

We found wheat-specific IgE in the RAST score range 0.5-4 in the sera of twenty-two (54%) out of forty-one children with eczema in patient group (c) (Table 3). Rye-specific IgE was determined in eight cases and five (63%) of these gave a positive result in the range 0.5-2. In one case rye-specific IgE (score 0.5) was found in the absence of wheat-specific IgE. As with the bakers, skin test results agreed best with other results (Table 4). Skin test and specific IgE results were identical in 79% of the cases, and this was the highest percentage for any two types of data.

Group (d) contained children with a similar age distribution, but representing the general population as far as allergy is concerned. One child (3%) out of thirty-four had a positive RAST score of 0.5.

We were unable to assemble a further age-matched group with allergic symptoms other than eczema. Instead we studied somewhat older children with rhinitis and

Table 2. Agreement among history, skin test, specific IgE and nasal challenge test results for asthmatic bakers belonging to patient group (a). When a single test result differed from all the others (e.g. skin test positive for wheat, with history, specific IgE and challenge negative for wheat) the differing result was classified as being in 'disagreement'. When an equal number of results were positive and negative, all were classified as 'uncertain'. Otherwise results were in 'agreement'. The history was always considered to be the same for both wheat and rye flour allergy, since these could not be reliably distinguished

History or test	Number of cases	Agreement (%)	Uncertain (%)	Disagreement (%)
History	42	55	24	21
Skin test	40	75	25	0
Specific IgE	42	71	24	5
Nasal challenge	40	63	25	13

Table 3. Patient group (c): forty-one children with eczema

Patient	Sex	Age*	Diagnoses†	Blood eosinophils ($\times 10^9/L$)	Serum total IgE ($\mu\text{g/ml}$)	Wheat flour				Rye flour			
						History	Skin test	Specific IgE (RAST score)	Oral challenge	History	Skin test	Specific IgE (RAST score)	Oral challenge
H.H.	F	5	E	180	<10								
E.P.	M	6	E	1340	120			0					
T.P.	M	9	E	570	900			0					
T.T.	F	1	E	90	30			3					
K.K.	F	1	E	700	60			0.5					
T.N.	F	1	E	350	30			0					
S.H.	F	1.5	E	240	100			0					
N.M.	F	1.5	E	350	50			0				0	
M.K.	F	1.5	E	300	50			0				0	
J.S.	M	1.5	E	90	750			0					
K.H.	M	1.5	E	350	100			0					
M.A.	M	1.5	E	70	16000			0					
P.O.	M	1.5	E	990	3200			2					
M.S.	F	2	E	1250	350			0					
A.P.	F	2	E	990	4000			0.3				0.5	
A.N.	F	2	E	240	60			0					
A.N.	F	2.5	E	410	300			0					
H.H.	M	2.5	A.E	770	1500			1					
J.R.	M	3	A.E	810	12000			2					
K.S.	M	3	E	40	750			1				2	
J.K.	M	3	B.E	290	250			0					
N.J.	F	3	E	400	250			0.5					
P.B.	M	3	E	1100	500			0				0	
V.J.	M	3	A.E	640	4000			0					

T.S.	F	3	E	420	2500
E.I.	F	3	A. E	480	3800
P.J.	M	3	E	1320	9500
A.E.	M	3	E	200	90
J.T.	M	3-5	A. E. R	400	1000
P.K.	M	3-5	A. E	1610	4000
I.K.	M	3-5	E	510	230
J.T.	F	4	E	220	60
J.T.	M	4	A. E	590	4100
E.S.	M	4-5	E	400	1100
T.V.	F	5	E	330	1100
M.L.	F	5	E	460	10
A.K.	F	6	A. E. R	220	2200
P.M.	M	6	A. E	420	570
M.T.	F	7	A. E	620	4000
M.L.	M	10	E	640	2000
A.H.	F	10	A. E	1360	1000
Mean		3-ly		529	2016
Logarithmic mean				408	510

Table 3 (cont.)

--	0-5	-
--	2	-
--	3	-
--	0	-
--	2	-
--	2	-
--	0	-
--	0	-
--	1	-
--	0-5	-
--	1	-
--	0-5	-
--	4	-
--	0	-
--	2	-
--	1	-
--	1	-

* In years unless otherwise stated.

† See Table 1 for explanation of symbols.

‡ Age in months.

Table 4. Agreement among history, skin test, specific IgE and oral challenge test results for children with eczema belonging to patient group (c). Only wheat allergen results are included (see also Table 2)

History or test	Number of cases	Agreement (%)	Uncertain (%)	Disagreement (%)
History	41	54		
Skin test	28	64	37	10
Specific IgE	41	61	36	0
Oral challenge	41	59	27	15

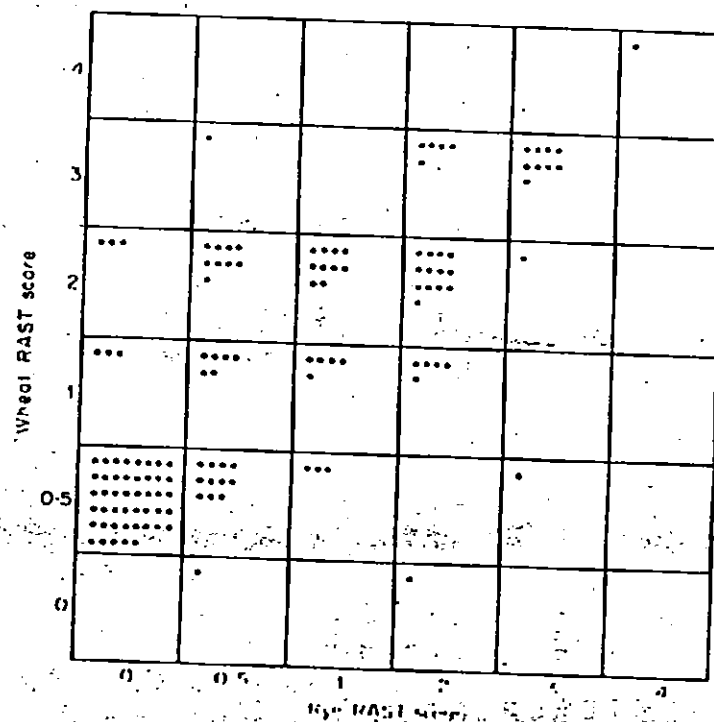


Fig. 1. Correlation between wheat- and rye-specific IgE concentrations. Data are given for 136 sera, each of which contained IgE antibodies against at least one of the antigens at a RAST score level of 0.5.

asthma in group (c). Two children (8%) out of twenty-four had a positive RAST score of 0.5.

Among ten children with coeliac disease, group (f), one (10%) had serum wheat-specific IgE at a level corresponding to a RAST score of 0.5. A second child was noted to have a serum total IgE concentration of 1400 μ ml, which is well above the normal range.

The correlation between wheat- and rye-specific IgE concentrations

We compared the concentration of wheat- and rye-specific IgE in the sera from 136

persons in group (g) (Fig. 1). In 60% of the sera both wheat- and rye-specific IgE was found, as indicated by a RAST score of at least 0.5 for each antigen. In 38% of the sera no rye-specific and in 1.5% no wheat-specific IgE was detected. The Spearman rank correlation coefficient for the RAST scores was 0.826 (significantly different from 0, $P < 0.001$), and the regression equation was:

$$[\text{wheat score}] = 0.698 [\text{rye score}] + 0.651.$$

Discussion

Wheat and rye flour contain about 10% protein, also called gluten. This protein includes a large number of separable protein species, which are traditionally grouped on the basis of solubility in gliadins, glutenins, albumins and globulins (Patey, 1974). Using crossed immunoelectrophoresis, Blands *et al.* (1976) demonstrated the presence of forty protein antigens in a wheat flour extract. In the sera of thirteen allergic bakers they found IgE against eighteen of these proteins, which belonged to the gliadin, albumin and globulin groups. Similar experiences in our laboratory led us to couple as many cereal proteins as possible to the solid-phase carrier used in our wheat and rye flour RAST.

Blands *et al.* (1976) also demonstrated that twenty of the wheat proteins cross-reacted with rye flour proteins. In analogy with this, we found that the wheat and rye flour RAST usually yielded correlating results. Our wheat RAST was more sensitive and the rye RAST was positive alone in only two out of 136 cases (Fig. 1). Thus determination of rye flour-specific IgE rarely provided information beyond that obtained by an assay of wheat flour-specific IgE.

Flour-specific IgE is frequently found in the sera of bakers with asthma (Table 1) or rhinitis (Blands *et al.*, 1976). In our hands, the RAST score was frequently only 0.5, but this has, for the present purposes, been considered as a positive test result. In fact, the score 0.5 is a marginal value, which we sometimes also encountered in children and adults with asthma or rhinitis, but with no history of wheat or rye allergy. We conclude that the RAST is useful in the diagnosis of allergy to inhaled wheat or rye flour dust.

Children with strong and unequivocal food allergies usually have high serum concentrations of IgE specific to the offending food proteins (Aas & Lundkvist, 1973; Hoffman & Haddad, 1974; Schur, Hyde & Wypych, 1974; Chua *et al.*, 1976; Dannaeus *et al.*, 1977). In our study, child A.K., 6 years old, had a wheat RAST score of 4 - the highest encountered (Table 3). She had a history of asthma caused by flour dust. An oral challenge with wheat caused diarrhoea and itching within 2 hr. Some years previously she had received a diagnosis of coeliac disease, which was probably erroneous and should have been cereal allergy. Child T.P., 9 months old, also had a strong and unequivocal reaction urticaria and swelling - upon oral challenge combined with a wheat RAST score of 3.

On the whole, however, the diagnosis and treatment of food allergies in children with eczema must be considered an unsolved problem. The RAST has brought only limited aid. The presence of food-specific IgE in the serum can frequently be demonstrated in the absence of any obvious sensitivity to the food in question. This has been shown for many foods, including wheat (Hoffman, 1975; Hoffman & Haddad, 1975; Dannaeus *et al.*, 1977), and it is also apparent from our results concerning wheat and rye (Table 3). Specific IgE to fish is an exception; it is rarely, if ever, encountered in

the absence of an unequivocal fish allergy (Dannaeus *et al.*, 1977). In our group of children with eczema, 51% had a positive wheat RAST score in the range 0.5-4 (Table 3). Of the twenty-two children with a positive score, only eight had a positive history or a positive challenge test result. In one case, a RAST score as high as 3 was accompanied by such negative data.

Among children from the general population, with a similar age distribution, and among children with allergic rhinitis or asthma, scores of 0.5 were occasionally encountered, while no higher scores were found. Thus cereal RAST scores above 0.5 were peculiar to children with eczema.

Six children with eczema had a positive history, or a positive challenge test, suggesting wheat hypersensitivity, but no IgE antibodies to wheat could be found in their sera. Neither the histories nor our challenge procedures were entirely dependable, and they may have been in error in some of these cases. We have the impression, however, that clinical reactions to wheat can occur in the absence of circulating IgE antibodies to wheat. Possibly allergens could be formed from cereals in the alimentary tract, which would explain the results.

The problem with eczematous children appears to be that they usually manufacture IgE antibodies against a large number of food antigens, some of which may be formed in the alimentary tract. The corresponding foods may or may not cause obvious symptoms. Finding all the offending antigens is difficult, and devising diets in which they are eliminated is still harder. There are, however, some cases in which the effects of one or a few foods predominate, and these can be treated with an elimination diet (Hoffman *et al.*, 1975).

It can be noted that the wheat RAST and the skin test results showed good agreement both in bakers and children (85% and 79% agreement respectively). Similar correlations have been noted for cow's milk, egg white and fish (Aas & Lundkvist, 1974; Schneeberger *et al.*, 1975). It is generally accepted that skin tests are of little value in the diagnosis of food allergies (Goldstein & Heiner, 1970). For many foods this may be true also for the RAST.

It should finally be mentioned that we also studied sera from ten children with biopsy-verified coeliac disease. One had a wheat RAST score of 0.5. In agreement with Heiner *et al.* (1970), we conclude that little or no circulating wheat-specific IgE can be found in such patients.

Acknowledgments

The study was supported by grants from Allergiatutkimussäätiö.

References

- AAS, K. & LUNDKVIST, U. (1973) The radioallergen sorbent test with a purified allergen from codfish. *Clinical Allergy*, **3**, 255.
- BLANDS, J., DIAMANT, B., KALLIÖ, P., KALLIÖ-DELFNER, L. & LOWENSTEIN, H. (1976) Flour allergy in bakers. I. Identification of allergenic fractions in flour and comparison of diagnostic methods. *International Archives of Allergy and Applied Immunology*, **52**, 392.
- BORCHERT, J. (1972) Beobachtungen über die Entwicklung des allergischen Asthmas und der allergischen Rhinitis bei Bäckern. *Acta allergologica*, **27**, 195.
- CISKA, M. & LUNDKVIST, U. (1972) A new and simple radioimmunoassay method for the determination of IgE. *Immunochimica*, **9**, 1021.
- CHOU, Y. Y., BRUMMER, K., TAKWALITA, N., FLORE, J. J., KOKORO, H. I., ORANIG, R. P. & COLLINS-WILLIAMS, C. (1976) *In vivo* and *in vitro* correlates of food allergy. *Journal of Allergy and Clinical Immunology*, **58**, 291.

- DANNAFUS, S., JOHANSSON, S.G.O., FOUCARD, T. & ÖRMAN, S. (1977) Clinical and immunological aspects of food allergy in childhood. I. Estimation of IgG, IgA and IgE antibodies to food antigens in children with food allergy and atopic dermatitis. *Acta paediatrica Scandinavica*, **66**, 31.
- GOLISTEN, G.B. & HEINER, D.C. (1970) Clinical and immunological perspectives in food sensitivity. A review. *Journal of Allergy*, **46**, 270.
- HEINER, D.C., GOLISTEN, G. & ROSE, H. (1970) Immunochemical studies of selected subjects with wheat intolerance. *Journal of Allergy*, **45**, 333.
- HENDRICK, D.J., DAVIES, R.J. & PEYS, J. (1976) Bakers' asthma. *Clinical Allergy*, **6**, 241.
- HJORTHISIER, H. (1973) The skin sensitivity to flour of bakers' apprentices. A final report of a long term investigation. *Acta allergologica*, **28**, 42.
- HOTIMAN, D.R. (1975) The specificities of human IgE antibodies combining with cereal grains. *Immunochimistry*, **12**, 535.
- HOTIMAN, D.R. & HADDAD, Z.H. (1974) Diagnosis of IgE-mediated reactions to food antigens by radioimmunoassay. *Journal of Allergy and Clinical Immunology*, **54**, 165.
- HOTIMAN, D.R., YAMAMOTO, F.Y., GILLER, R. & HADDAD, Z. (1975) Specific IgE antibodies in atopic eczema. *Journal of Allergy and Clinical Immunology*, **55**, 256.
- JOHANSSON, S.G.O., BENNICHT, H. & BERG, T. (1971) *In vitro* diagnosis of atopic allergy. III. Quantitative estimation of circulating IgE antibodies by the radioallergosorbent test. *International Archives of Allergy and Applied Immunology*, **41**, 443.
- LISKO, E. (1947) On allergic rhinitis and bronchial asthma in bakers. *Annales medicinar internae Fenniae*, **36**, 98.
- NAKAZAWA, T., TOYODA, T., FURUKAWA, M., FAYA, T. & KOBAYASHI, S. (1976) Inhibitory effects of various drugs on dual asthmatic responses in wheat flour-sensitive subjects. *Journal of Allergy and Clinical Immunology*, **58**, 1.
- PATEY, A.L. (1974) Gliadin: the protein mixture toxic to coeliac patients. *Lancet*, **i**, 722.
- ROWE, D.S., GRAH, B. & ANDERSON, S.G. (1973) An international reference preparation for human immunoglobulin E. *Bulletin of the World Health Organization*, **49**, 320.
- SCHNEIDER, H.-W., SCHERT, E., STEINHAUSEN, D. & FORCK, G. (1975) Die Bedeutung des Radioallergosorbentest (RAST) im Vergleich mit den Intrakutantest bei der Diagnose allergischer Erkrankungen. *Acta allergologica*, **30**, 411.
- SCHUR, S., HYDE, J.S. & WYPPYCH, J.J. (1974) Egg-white sensitivity and atopic eczema. *Journal of Allergy and Clinical Immunology*, **54**, 174.
- WILSON, R.D. & WARD, G.W. (1976) Immunological studies in a case of baker's asthma. *Journal of Allergy and Clinical Immunology*, **58**, 366.

Int. Archs Allergy appl. Immun. 52: 392-406 (1976)

Flour Allergy in Bakers

I. Identification of Allergenic Fractions in Flour and Comparison of Diagnostic Methods

J. Blands, B. Diamant, P. Kallós, L. Kallós-Deffner and H. Løwenstein

Medical Department TA, Rigshospitalet, Department of Pharmacology and Protein Laboratory, University of Copenhagen, Copenhagen

Abstract. Extract of wheat flour obtained by extraction, centrifugation and dialysis was immunochemically characterized by quantitative immunoelectrophoresis using rabbit antibodies. The analysis revealed wheat flour to be composed of 40 antigens, some of which were immunologically partially identical with antigens of rye flour and of common grass pollen. Furthermore, antigens of the gliadin fraction of wheat flour were identified.

25 bakers with allergic complaints working in and around Copenhagen were clinically tested with wheat flour and related extracts. Among 13 bakers with respiratory complaints (asthma and/or rhinitis), 11 showed positive reactions to wheat flour extract when tested in histamine release from basophil leukocytes radioallergosorbent test and skin test, whereas further 2 were positive in the basophil test only.

The ability of the IgE of individual sera to adsorb to the individual antigens of wheat flour was examined by means of crossed radioimmuno-electrophoresis. On the basis of these results, individual allergenic components of wheat flour were identified, three of these with comparatively high affinity and frequency.

Introduction

Bonnevie [1958] pointed out that the 'founder of modern occupational medicine, Ramazani' as early as in 1700 wrote that 'bakers were often diseased by cough, shortness of breath and hoarseness'. Later on, these respiratory disorders have been diagnosed as rhinitis and/or bronchial asthma. According to Bonnevie, the etiology of

these occupational diseases, allergy to wheat and/or rye flour, has been established by Schloss [1916], who obtained positive immediate skin reactions in asthmatic bakers with 'ordinary wheat extract'. These early findings were confirmed and extended for example by Baagø [1933], Castberg and Sørensen [1948], van Dishoeck and Roux [1939], Schwartz [1952], Gadborg [1956], Diedrichs and Lübbers [1955], and Pesta-

Received: September 10, 1976

Blands/Diamant/Kallós

lotzi and Schnyder 1929, de Besche reported passive transfer of allergy to Prausnitz-Küstner asthmatic bakers allergic to wheat flour that 'these cases are allergic asthma, acquired the influence of specific work (i.e. exposition seems to be justified order as occupational disease' (translation).

From 1952 to 1971 Deffner [1971] investigated. Based on anamnesis, symptoms, the results of skin provocation [1946] with flour extract diagnosed in 163 of the affected cases) (48%) rhinitis and 16% (Kallós-Deffner [1971]) without typical clinical signs, a positive skin or provocation test to wheat flour extract. 85 of the bakers allergic to wheat flour and 37 (23%) to be their occupational disease and asthma due to wheat rye pollen extract. In this group a positive skin test to the flour-allergic baker's other cereal product provocation to flour occurred within the 1st year. 76.7% of the cases between the 2nd and 3rd year of professional activity. This was explained [Marsh, 1971] Rhinitis was in a severe, and asthma occurred.

International Archives of Allergy and Applied Immunology
52, 1976
AK-117057

lozzi and Schnyder [1955]. As early as 1929, *de Besche* reported on the successful passive transfer of skin reactivity (according to Prausnitz-Küstner) with the serum of 3 asthmatic bakers and 3 grain workers allergic to wheat flour. *De Besche* concluded that 'these cases are to be regarded as allergic asthma, acquired by individuals under the influence of special conditions in their work (i.e. exposition to flour dust). Thus, it seems to be justified to characterize this disorder as occupational disease, namely baker's disease' (translated by us).

From 1952 to 1971, *Kallós* and *Kallós-Deffner* [1971] investigated 583 bakers. Based on anamnesis, clinical signs and symptoms, the results of skin testing and nasal provocation [*Urbach and Gottleb*, 1946] with flour extract, flour allergy was diagnosed in 163 cases (30%). 85 (52% of the affected cases) had rhinitis only, 78 (48%) rhinitis and asthma. *Kallós* and *Kallós-Deffner* [1971] obtained in no case without typical clinical signs and symptoms a positive skin or provocation test with flour extract. 85 of the reactors (53%) were allergic to wheat flour, 41 (25%) to rye flour, and 37 (23%) to both. 4 cases had, besides their occupational disease, seasonal rhinitis and asthma due to grass pollen. Wheat or rye pollen extract elicited in no case within this group a positive skin reaction. All of the flour-allergic bakers could eat bread and other cereal products with impunity. Sensitization to flour occurred in 38 cases (23.3%) within the 1st year in the profession. In 76.7% of the cases, sensitization occurred between the 2nd and 15th year of professional activity. This discrepancy cannot be explained [*Marsh*, 1975].

Rhinitis was in all cases the initial disorder, and asthma occurred in about half of

the cases 6 months to 10 years later. These observations are in good accordance with the literature. Continuous exposition to flour dust leads in individuals with hereditary disposition to sensitization and allergic disease [*Marsh*, 1975]. The best prophylactic measure is to diminish or eliminate this exposition. According to *Kallós* and *Kallós-Deffner* [1971], the frequency of sensitization is clearly decreasing in modern bakeries, where flour is handled in a completely closed system.

Kallós and *Kallós-Deffner* [1971] used freshly prepared conventional flour extract (*Coca's* solution, 1:10 w/v, undiluted for nasal provocation, appropriately diluted for skin tests) in their investigations. They showed that allergenic activity is confined to the protein fraction of flour extract.

In a recent investigation, *Hoffmann* [1975] analyzed the inhibitory effect of different protein fractions of wheat and whole wheat extracts as well as the cross-reaction between grass pollen and wheat flour by means of the radioallergosorbent test (RAST). He found generally a low cross-reactivity between grass pollen and wheat flour. Among the wheat protein fractions studied, the highest reactivities (i.e. allergenicity) were found in the most soluble fractions.

In the present investigation, we attempted to evaluate the histamine liberation induced by wheat flour extract from basophil leukocytes in a group of allergic bakers and appropriate controls and to correlate the results to the clinical state of the patients as well as to their skin reactivity, and to the results of *in vitro* tests such as radioimmunosorbent test (RIST) and RAST with flour extract. Finally, the protein fraction of flour extract has been analysed by means of

anodic and cathodic second dimension gel was used (fig. 1). Unless otherwise stated, first- and second-dimension electrophoreses were performed in a 0.15-cm-thick gel at 10 Vcm⁻¹ for 30 min and in 0.10-cm-thick gel at 2 Vcm⁻¹ for 15 h, respectively. 7×5 cm glass plates were used for CIE and CLIE. The thickness of the intermediate gels was 0.12 cm. 1% (v/v; relative to the antibody volume) of Aprotinin (Novo, Mainz, BRD) was added to the antibody-containing gels to prevent proteolytic degradation [Bjerrum *et al.*, 1975]. The plates were pressed, washed, and dried, and finally stained with Coomassie Brilliant Blue R as described by Weeke [1973].

CRIE

CRIE was performed as described by Weeke and Löwenstein [1973]. The procedures performed at room temperature (18–24 °C) were briefly as follows: (1) Incubation with patient serum: 7 ml of 1/15 M phosphate buffer (pH 7.5) and 0.7 ml of serum added to the plastic box was sufficient to cover the gel film on the glass plate; (2) after being left to react overnight, the non-bound serum proteins were removed from the gel by washing it with 10–20 ml of 0.1 M sodium chloride at least four times for 10-min periods; (3) ¹²⁵I-anti-IgE in 7 ml of incubation buffer (0.05 M phosphate buffer, pH 7.5, containing 0.3% (w/v) of bovine serum albumin, 0.9% w/v sodium chloride, 0.1% w/v of sodium azide, and 1% w/v of EDTA), corresponding to 0.35 μ Cl and giving rise to approximately 200,000 cpm in our gamma-counter, was added to the gel and allowed to react for at least 1 day; (4) nonbound ¹²⁵I-anti-IgE was recovered and stored for later experiments; (5) after 4 10-min washings with 10–20 ml saline and finally 1 washing with distilled water, the gel on the glass plate was dried in hot air and placed on an X-ray film in a light-proof box. The exposure time was varied from 1 day to 2 months, and (6) the gel on the glass plate was stained for proteins with Coomassie Brilliant Blue.

Autoradiography

Autoradiography was performed as described by Löwenstein *et al.* [1976] by measuring the exposure time necessary for visible radiostaining of the various precipitates. The periods of exposure spanned days 0–1, 1–7, and 8–43, which, after

correcting for the radioactive decay of ¹²⁵I, amounted to 1, 6.7 and 26.8 days. The activity bound to the various precipitates was graded 27, 4, and 1, respectively (normalized reciprocal values of the corrected exposure times), corresponding to visible radiostaining after 1, 8, and 43 days. In case of very strong radiostaining, the grading was multiplied by factor 2. The values obtained were further corrected for the mean unspecific IgE uptake in wheat CRIE performed on 4 non-allergic and 5 non-flour-allergic subjects.

RIST

Phadebas IgE (Pharmacia) was used for the determination of total IgE in the analyzed sera. The total IgE concentrations were expressed in Uml⁻¹ by comparison with a WHO standard serum [Rowe, 1971]. 1 U corresponds approximately to 2.4 ng [Bazara and Hamburger, 1972]. The reproducibility of the determinations was about 10%. We took a value of 26–630 Uml⁻¹ as being a normal 95% range in adults.

RAST

RAST was performed with St MS 74, coupled to activated filter paper discs according to Ceska *et al.* [1972]. The results were expressed in sorbent units (SU) and in allergy classes (class 0, 1, 2, 3, and 4, corresponding to 0–1, 2–3, 4–19, 20–99 and ≥ 100 SU, respectively), using the reaction of the serum (diluted $\times 10$) from a patient (H. D.) allergic to timothy as a 100 SU reference. The grading system corresponds to that for Phadebas RAST (Pharmacia) reference (birch allergen and birch allergic reference serum). The determinations were performed in duplicate.

The duplicate determinations were run twice for each serum and the mean values were used.

RAST Inhibition Experiments

They were performed as described by Nielsen *et al.* [1974] and the concentrations corresponding to a 50% inhibition (C₅₀) were measured.

The inhibition experiments were performed with gliadin 1%, having dilutions from 1 to 10⁻⁶ in steps of 1 decade. St MS 74 was used as the allergen reference in the experiments. Sera from the patients listed in table I were used.

Intracutaneous tests (IC)

They were carried out on the volar side of the

antebrachium, using a histamine dihydrochloride solution (0.1 mg ml^{-1}) as a reference. St MS 74 (wheat flour) dissolved in 0.9% sodium chloride, 0.5% phenol (w/v) and diluted $\times 10^4$ – 10^6 was used for the skin testing. The dilutions were carried out less than 1 month before performing the tests. The area of the urticarial wheal was determined by multiplying the mutually perpendicular diameters (in millimeters). According to the Scandinavian Allergy Standard [Aas and Belln, 1972] a 3+ reaction corresponds to 1 histamine equivalent. In some cases, St Ru 75 (rye flour) was tested using similar criteria.

IC St MS 74 $\times 10^{-4} \text{ mm} \times \text{mm}$ — skin test index —
IC histamine, $0.1 \text{ mg ml}^{-1} \text{ mm} \times \text{mm}$
was used when compared with the various *in vitro* tests.

Separation of the Leukocyte Fraction from Whole Blood

The procedures follow in general the methods described by Bøyum [1968] and Day [1972]. 9 ml venous blood was collected in a plastic tube (volume 10 ml) containing EDTA (0.5 ml of a 0.2 M solution). After gentle mixture, 7.5 ml was diluted with 22.5 ml NaCl (0.9%) in a 50 ml plastic tube. Sodium diatrizoate (10.3% w/v; Winthrop Laboratories Ltd., Surrey, England) or in most experiments sodium metrizoate (10.5% w/v; Nyegaard AS, Oslo, Norway) mixed with Ficoll (6.4% w/v) and adjusted with distilled water to a specific gravity of 1.080 was used as separation fluid. 11 ml of the separation fluid was layered below the blood suspension with care taken to maintain a sharp interphase. The tube was centrifuged at 400 g for 40 min at room temperature. The interphase containing leukocytes was harvested by the use of a Pasteur pipette. The cell suspension was diluted with 10 ml of a balanced salt solution (BSS) containing 131 mM NaCl, 2.4 mM KCl, EDTA 1 mM and 1 mg/ml human serum albumin buffered to pH 7.0 with Spørensen phosphate buffer (6.7 mM). The cells were washed twice by centrifugation for 10 min at 70 g. They were finally diluted in 150 μl of the same BSS, except that EDTA was exchanged for 1.5 mM CaCl_2 .

Incubation Procedures

5 μl of the cell suspension was added to 200 μl

prewarmed (37°C) calcium-BSS containing suitable dilutions of the antigens. Routinely, the antigens (wheat and rye flour extracts free of azide) were tested in dilutions 10^{-2} – 10^{-10} . Each dilution was run in triplicate.

Incubation was performed in small glass tubes (OD 7 mm, ID 5 mm, length 50 mm) for 30 min at 37°C . The tubes were then placed on ice and centrifuged for 10 min at 600 g at 4°C . The supernatant was transferred by the use of a constriction pipette to new tubes containing 5 μl of 3 N HCl. The cell residues were placed on a boiling water bath for 5 min after the addition of 200 μl of distilled water and 5 μl of 3 N HCl. In each experiment, the spontaneous histamine release was determined as well as possible blank values for the highest concentration of antigens.

Histamine Determination

To each supernatant and precipitate 30 ml 1.25 N NaOH was added followed by 10 μl orthophthalaldehyde (1% dissolved in methanol). After exactly 4 min, 10 μl of 3 N HCl was added to the tubes. Vigorous mixing was performed after each addition. Following centrifugation for 10 min at 2,500 g, the fluorescence was read in a Farrand Ratio Fluorometer supplied with a Farrand carrier and adaptor suitable for the small incubation tubes used.

Histamine release was determined as a percentage of the total histamine content of each sample. Although the maximal release could vary between different individuals, the concentration of the antigen solution which released 50% of the maximum values was determined after graphic registration of the results. In some cases, it was necessary to decrease the antigen concentration below 10^{-4} to obtain this value.

Storage of Blood Samples

For convenience it was of interest to determine if blood samples could be stored 12–24 h before separation of the leukocytes without loss of reactivity or cells. This was determined in 5 cases. Duplicate blood samples were stored overnight at 4°C before separation and incubation. In 4 cases, identical release values and similar histamine content of the separated cells were found for stored blood as compared to blood immediately used for



Fig. 1. Extract of wheat flour in 1% (w/v) agarose gel. Tris, 0.024 M barbital, 0.006 M and 0.0003 M sodium azide (pH 7.5). Antigens: 10 μl of St MS 74 applied. First dimension: 10 V/cm thick gel for 25 min. Anode to the left: 20 μl cm^{-2} , rabbit antiserum to wheat flour. Second dimension: 0.10-cm-thick anodic (+) and

separation and study of the reaction. The reason why one of the blood samples gave similar results after storage was not established. At present, however, cannot be excluded.

Statistical Evaluation of Correlation. Rank difference coefficient r_s determined between the results of the two tests and is given in the text.

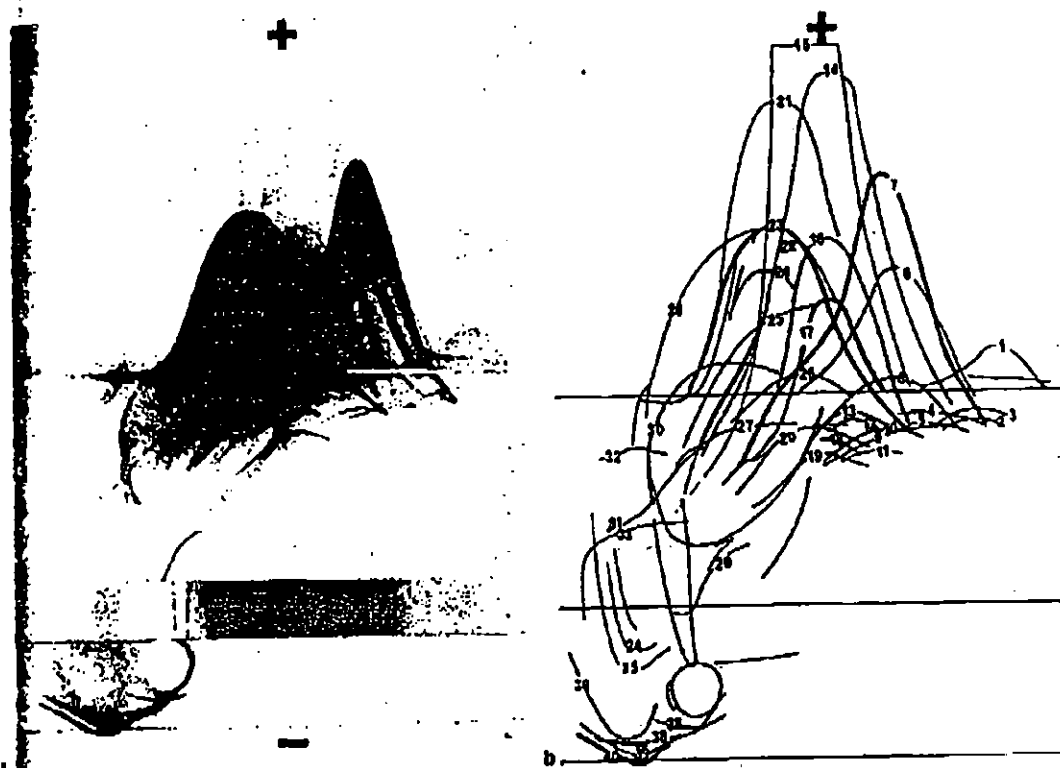


Fig. 1. Extract of wheat flour examined by CIE in 1% (w/v) agarose gel containing 0.073 *M* Tris, 0.024 *M* barbital, 0.006 *M* calcium lactate and 0.0003 *M* sodium azide (pH 8.6, 25 °C) at 15 °C. a Antigens: 10 μ l of St MS 74 DF was applied. First dimension: 10 V cm^{-1} in a 0.15-cm-thick gel for 25 min. Anode to the right. Antibodies: 20 μ l cm^{-1} , rabbit antibodies against extract of wheat flour. Second dimension: 2 V cm^{-1} in 0.10-cm-thick anodic (+) and cathodic (-) gels

for 15 h. Intermediate gel: a 0.12-cm-thick gel containing 20 μ l of 0.1 *M* sodium chloride per cm^2 . Agarose gel electrophoresis: Superimposed by photomontage on the first dimension gel: 10 μ l of St MS 74 DF was applied; experimental conditions were as for the first-dimension electrophoresis. b A drawing of the same CIE precipitation pattern of St MS 74. Classification numbers for the precipitates are indicated.

Results

CIE Analysis of Allergen Extracts

Agarose gel electrophoresis of St MS 74 DF revealed at least 12 different bands of which 6 migrated against the anode and 6 against the cathode. This is illustrated in figure 1, together with the reference precipita-

separation and study of the reactivity of the cells. The reason why one of the blood samples failed to give similar results after storage remains to be established. At present, however, a technical error cannot be excluded.

Statistical Evaluation of Correlations

Rank difference coefficient of correlation was determined between the results of the various clinical tests and is given in the text.

Table I. Identity/partial identity of antigens from wheat flour with antigens of rye flour, wheat gliadin, and pollen from timothy, rye grass, blue grass, false oat and orchard

Anti- gen No.	Wheat gli- adin	Rye flour	Timo- thy	Rye grass	Blue grass	False oat	Or- chard
1	+	+	+		+	+	+
2		+	+			+	
3		+					
4							
5							
6		+	+		+	+	+
7		+					
8		+	+		+	+	+
9							
10							
11							
12		+					
13		+					
14		+					
15							
16	+	+					
17	+	+					
18							
19		+	+	+	+	+	+
20		+					
21		+	+	+			
22		+					
23	+	+					
24							
25							
26		+	+		+	+	+
27		+					
28	+	+					
29							
30	+	+					
31							
32							
33							
34							
35							
36							
37							
38							
39							
40							

tion pattern obtained by CIE of St MS 74 DF. About 30 immunoprecipitates were revealed in the second-dimension gel (fig. 1). A few additional weak precipitates were demonstrated using various concentrations of antigens and antibodies giving a total of 40 precipitates. The precipitates were arbitrarily numbered from 1 to 40. Antigens 1-28 and 31-33 precipitated in the anodic antibody-containing gel, antigens 34-40 in the cathodic antibody-containing gel, and antigens 19 and 30 in both gels. Antigen 16 was found to be partially identical with antigen 19, antigens 24 and 28 to 23, and antigens 34, 35, 38 and 39 to 40. Comparison between St MS 74, St MS 74 DF and the supernatant and the dialyzed extract obtained during the preparation of St MS 74 DF using CIE revealed the 4 extracts to be qualitatively identical.

Comparisons between antigens of wheat flour and those of rye flour and gliadin and from 5 grass pollens are shown in table I. The comparison was carried out by means of CLIE. 6 antigens of St MS 74 DF (1, 16, 17, 23, 28 and 30) were shown to be contained in gliadin. St Ru 75 contained 20 antigens partially identical to antigens 1-3, 6-8, 12-14, 16, 17, 19-23, 26-28, and 30 of St MS 74 DF. All of the recognizable antigens of gliadin were also contained in St Ru 75. Antigens 1, 2, 6, 8, 19, 21, 26 showed partial identity with antigens of grass pollen extracts. Antigens 3, 13, 16, 23, 24, 27 and 28 of timothy pollen [Nielsen *et al.*, 1974] were partially identical to antigens of wheat flour.

CRIE was performed to identify the allergens of wheat flour. Data for sera from 25 patients are shown in table II and the CRIE analysis in table III. The latter table also includes the mean of the results of

Table II. Clinical and

Table II. Clinical and

No.	Years in prof.	Asth- ma	Rhini- tis
1	14		+
2	5		+
3	36		
4	16		
5	21		
6	15		
7	21		+
8	15		+
9	18		+
10	41		+
11	38	+	+
12	25		+
13	18	+	+
14	50	+	
15	24		+
16	8	+	+
17	35		
18	21		+
19	46	+	+
20	6		+
21	35	+	
22	38	+	
23	44		+
24	40	+	
25	39	+	

ND = Not done.

CRIE from individuals of allergy (controls) and to wheat or rye flour used as blanks and from the corresponding individuals mentioned. Data were arranged in histamine release and patients releasing histamine of IgE in the value to the other patients (1, 5, 7, 10-1

Table II. Clinical and test results of the individual patients

No.	Years in prof.	Asth- ma	Rhino- itis	Hay fever	Urti- caria	Ecze- ma	Treat- ment	Skin test 0-3+	Skin index 10 ⁻⁴	RAST units	class	Total IgE ng/ml	Hist. rel.	Summed CRIE points
1	14		+	+			+	3+	0.85	50	3	408	5×10^{-6}	23
2	5		+			+	+	-		3	1	21	-	8
3	36				+		+	-		<1	0	247	-	ND
4	16					+	-	-		1	0	56	-	9
5	21			+			+	3+	0.83	100	4	2,172	5×10^{-4}	10
6	13					(+)	-	-		<1	0	210	-	2
7	21		+	+		+	(+)	3+	0.80	14	2	68	5×10^{-5}	2
8	15		+			+	+	-		3	1	23	-	5
9	18		+				+	-		5	2	93	-	1
10	41		+				+	1+	0.19	2	1	44	10^{-5}	6
11	38	+	+				+	?	0.25	14	2	51	5×10^{-6}	10
12	25		+				-	3+	0.82	33	3	924	5×10^{-4}	16
13	18	+	+			+	-	3+	0.47	69	3	231	10^{-5}	40
14	30	+		+			-	3+	0.74	63	3	124	10^{-5}	62
15	24		+				(+)	2-3+	0.75	105	4	2,169	5×10^{-7}	23
16	8	+	+				+	-		1	0	91	-	5
17	35					+	+	-		1	0	49	-	0
18	21		+			+	-	3+	0.79	53	3	504	5×10^{-6}	26
19	46	+	+				(+)	1+	0.36	6	2	119	10^{-5}	0
20	6		+			+	(+)	1+		2	1	204	-	ND
21	35	+					+	-		<1	0	38	-	8
22	38	+					-	2+	0.11	1	0	72	5×10^{-4}	3
23	44		+			+	-	2+	0.57	60	3	608	10^{-7}	32
24	40	+				+	+	-		2	1	137	-	3
25	39	+					+	-		<1	0	41	-	0

ND = Not done.

CRIE from individuals without any history of allergy (controls) and patients not allergic to wheat or rye flour. These values were used as blanks and have been subtracted from the corresponding values of the allergic individuals mentioned in table III. The data were arranged in descending order of histamine release and it is seen that all the patients releasing histamine have a high uptake of IgE in the various precipitates relative to the other patients. Based upon 13 patients (1, 5, 7, 10-14, 17-19, 22 and 23)

allergic to wheat flour, it was shown that 18 different immunoprecipitates revealed affinity to IgE from the patients (fig. 2). 12 of the immunoprecipitates showed high affinity (fig. 2; antigens 1, 7, 15-17, 20-23, 26-28) and among these 3 immunoprecipitates extremely high affinity (table III; antigens 7, 23 and 28). The incidence for IgE affinity among the immunoprecipitates was rather low. Taking both incidence and degree of affinity into consideration, the most significant allergens of wheat flour were antigens

Lowenstein

Wheat Allergy in Bakers I

401

amine release

wheat flour

Antigen No. *

3 14 15

16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40

2
3

3 1 2 17 2 2 26 2 2

8

7 1 4 8

3

3 1 8 3 8 3 3

2

1 1 8 2 3 3 3

3

1 1 3 3 3 3

3

3 1 1 1 3 3 3

3

1 1 3 3 3 3

3

1 1 1 1 3 3 3

1

1 1 1 1 1 1 1

Mean of two CRIE experiments.

Mean of specific IgE binding to the individual antigens of wheat flour, for control individuals without any history of allergy or with allergy to anything different from wheat flour.

text.

patients

gliadin
in the
inhibition
of gliadin

Basophil Tests Related to Subjective Symptoms, Skin Tests, RAST and CRIE

Individual data for each subject investigated are presented in table II. A typical response curve for the reactivity of the basophils from a sensitive subject against wheat and rye flour is shown in figure 3. 13 of the

bakers tested reacted with histamine release from the basophilic granulocytes when exposed to wheat allergen, but 12 were completely negative. 12 of the bakers were additionally tested with rye flour as allergen; 6 of these were negative to rye flour, and 6 were positive. In each case, a positive or

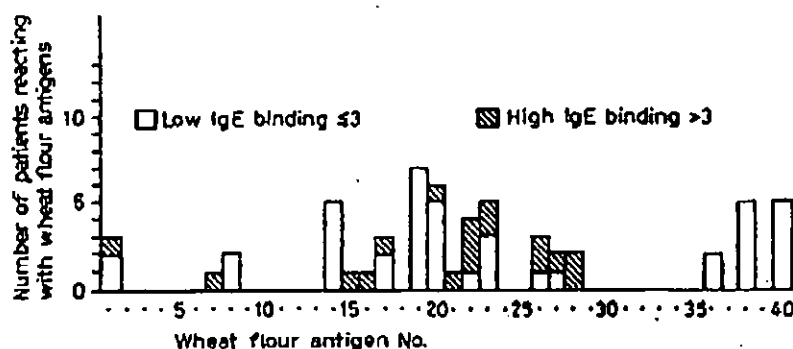


Fig. 2. Allergogram for antigens of wheat flour based upon sera from 13 patients positive in the basophil test to wheat flour extract. Specific IgE binding to the individual antigens was obtained by means of CRIE. The extent of IgE binding was evaluated visually from the autoradi-

ographs of the CRIE plates. Radiostaining visible after 8 days was taken to indicate a high degree, and staining after more than 8 days was taken to indicate a low degree of IgE binding. See text for further explanation.

negative response towards rye flour corresponded with the results for wheat flour. The maximal release (percentage of total histamine content) varied between different individuals, as did the concentration of allergen eliciting 50% of the maximal histamine release. In 12 of the positive subjects, the maximal release observed was between 50 and 70% of the total histamine content of the cells. In the remaining case, maximal release did not exceed 40%.

The symptoms described by the bakers correlated with the basophil test and are shown in table IV. 22 of the bakers complained of various symptoms indicating immediate type of allergy, and 7 of these had eczema, too. The remaining 3 had eczema alone without other symptoms. In the questionnaire, the bakers had a possibility of giving information as to what allergen they personally suspected. 12 of the bakers suspecting wheat flour were positive in the basophil test to this allergen, and one additional subject, who did not suspect wheat

flour, was, however, found to react positively. Among the 12 bakers who were found to be negative in the basophil test, 6 suspected wheat flour to be the cause of their symptoms, and the remaining 6 suggested other agents (or none at all) to be the possible allergen. It can be seen that 3 bakers who had eczema as a single symptom were all negative in the basophil test, RAST, as well as immediate skin reactivity. When the skin reactivity (skin index) and the basophil test were compared (table II), no statistically significant correlation ($p > 0.05$) was found between the two tests. Provided the skin index is considered positive above 0.25, 2 of the bakers (patients 10 and 22), who were positive in the basophil test, were negative in the skin test. In all cases, a positive skin index was accompanied by a positive basophil test. The correlation between the basophil test and RAST was not statistically significant ($p > 0.05$; table II). When a negative RAST is considered below 4 SU, the same bakers (10 and 22) would also be negative

Flour Allergy in Bakers

Table IV. Classification of the patients according to liberation test and the patients of wheat flour according to the question

Allergic disorder

Asthma
Asthma + rhinitis
Asthma + rhinitis + eczema
Asthma + eczema
Rhinitis
Rhinitis + eczema
Eczema
Urticaria
Total

The results represent
+ = Suspected wheat flour
- = did not include wheat flour
0 = did not suggest any al

from the RAST test, test was positive. In RAST observed with test. A significant correlation found between the b (table II).

Discussion

Immunochemical

The antigenic correlation has been investigated by immunoelectrophoretic rabbit antiserum to wheat flour. The analysis has revealed 40 different components. However, at this sta

Table IV. Classification of the allergic disorders of the patients according to the results of the histamine liberation test and the subjective opinion of the patients of wheat flour being the causative agent (according to the questionnaire)

Allergic disorder	Histamine liberation test			
	positive		negative	
	+	- or 0	+	- or 0
Asthma	1		2	1
Asthma + rhinitis	1	1	1	
Asthma + rhinitis + eczema	1			
Asthma + eczema			1	
Rhinitis	6			1
Rhinitis + eczema	3		1	1
Eczema			1	2
Urticaria				1
Total	12	1	6	6

The results represent the number of patients. + = Suspected wheat flour as possible allergen; - = did not include wheat flour among suspected allergens; 0 = did not suggest any allergen.

from the RAST test, although the basophil test was positive. In no case was a positive RAST observed without a positive basophil test. A significant correlation ($p < 0.01$) was found between the basophil test and CRIT (table II).

Discussion

Immunochemical Analysis

The antigenic composition of wheat flour has been investigated using quantitative immunoelectrophoretic methods employing rabbit antiserum to whole wheat extract. The analysis has revealed wheat flour to contain 40 different antigens, some of these showed partial immunological identity. However, at this stage of the investigation,

other immunochemical connections between the various antigens cannot be excluded. These may be revealed by analysis with partially purified protein fractions of wheat flour. A possible explanation of the partial identity of the antigens might be proteolytic and/or physicochemical degradations during grinding and extraction.

The extraction of the protein from wheat flour was based on the assumption that only those which are soluble under moderate physiological conditions (i.e. ionic strength 0.1-0.25 and pH 5.0-9.0) have the ability to act as allergens *in vivo*. About 80% of the protein in wheat flour belong to the water-insoluble gluten fractions (i.e. ethanol-soluble gliadin and acid or alkaline-soluble glutenin) and therefore lack allergenic activity unless under extreme local physicochemical conditions which might exist in tissues where sensitization occurs. Thus, the possibility cannot be excluded that the extract used in our investigations does not contain all allergens which may act *in vivo*. However, repeated washing and centrifugation of commercially available gliadin revealed that a soluble fraction occurred in each washing, and this was quantitatively and qualitatively identical. The rest is completely soluble in 50% (v/v) ethanol. This solution has a similar antigenic composition as the water-soluble fractions obtained by washing [Lowenstein, unpubl.].

The low solubility of gliadins is demonstrated by the result obtained in the Lowry determinations which also makes it plausible that gliadin (1%) does not contain proteins unrecognizable by means of the rabbit antibodies we used.

All 6 antigens of gliadin were identified in both wheat and rye flour, and the latter extract contains a further 14 antigens parti-

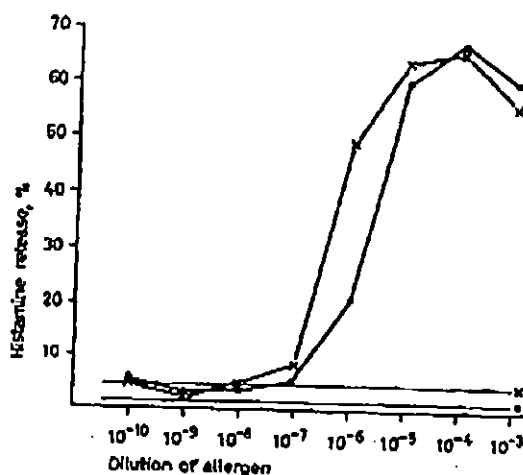


Fig. 3. Histamine release from basophil leukocytes of patient 18 induced by wheat flour (X) and rye flour extract (●).

ally identical with those of wheat flour. One antigen of wheat gliadin was partially identical with one grass pollen antigen which occurs in different grasses (table I). A further 6 antigens of wheat and rye flour extract were partially identical with grass pollen antigens, among which, in a recent study on timothy pollen, four have been shown to be allergens [Weeke *et al.*, 1974; Löwenstein *et al.*, 1974]. A high degree of partial identity exists between rye and wheat flour and the basophils of the patients investigated responded similarly to whole extracts of both. However, the possibility still exists to demonstrate allergenic proteins in rye not contained in wheat extract and vice versa.

The specificity of IgE from the various patients demonstrates the variation of the individual immune response. As discussed above, it is probable that the most soluble antigens show the highest IgE uptake, as demonstrated by us. In spite of our expectations, a high IgE uptake also occurred for

the less soluble proteins of gliadin (i.e. antigens 16, 23 and 28 in patients 14, 23 and 13). Only in case of patient 14 was it possible to verify by means of RAST inhibition that these gliadin proteins were allergenically active. This may be explained by the fact that gliadin proteins have low contents of lysine and, therefore, contribute in the RAST to a relatively low degree compared with the soluble proteins with higher lysine content. When patients (as 23 and 13) have specific IgE against both a highly soluble antigen and a gliadin antigen, the inhibition by means of the purified gliadin fraction may be masked. This might explain the discrepancies in the results obtained by Hoffmann [1975] who, by means of RAST, showed that gliadin protein is less active as an allergen than are those obtained by Goldstein *et al.* [1969] who used skin tests for studying the allergenicity of gliadin.

None of the patients studied by us stated that they were allergic against grass pollen, but 5 of them showed high IgE binding to antigens 1, 21, and 26, which are partially identical with pollen antigens. The possible clinical significance of this result can be evaluated by means of skin tests and/or basophil test using pollen extracts. A recent study among bakers' apprentices by Herxheimer [1973] indicated that subjects allergic to pollen more frequently than others became sensitized to wheat flour. On the other hand, Hoffmann [1975] found, by means of RAST, a low cross-reactivity between IgE from patients allergic to cereals and grass pollen. However, the possibility still exists that the allergenic site is not included in the same parts of the molecules.

Of the 40 proteins present in whole wheat extract, 3 (22, 23 and 28) were characterized as major allergens (table III). Iso-

lation and che
these is an impor

On the basis
is, it is not possi
tion of a mixture
consideration in
some lines of app
the results in tabl
ing (fig. 3) was fo
allergens of gliadi
5, 7, 10, 11, 15)
wheat flour only,
13, 18 and 23) to

Correlation bet

Of special inter
the basophil test g
positive results of
status of the patie
clinical symptoms
(rhinitis and/or as
sophil test; in co
group (10 and 22
RAST test with v
tients with rhinitis
ing wheat flour as
negative results w
In the 13 positive
ative correlation
three tests used (ta
to the results of N
tients with ragweed

Flour allergy is
disorder in bakers,
and reliable *in vitr*
great importance.
Recently been autom
[Straganlan, 1974]
used instead of a
method should be
diagnostic test in
testing exposes the

lation and chemical characterization of these is an important future aim.

On the basis of the present CRIE analysis, it is not possible to define the composition of a mixture of allergens preferable for consideration in immunotherapy. However, some lines of approach can be derived from the results in table III. Thus, high IgE-binding (fig. 3) was found (a) in 1 patient (14) to allergens of gliadin only; (b) in 6 patients (1, 5, 7, 10, 11, 15) to the soluble allergens of wheat flour only, and (c) in 4 patients (12, 13, 18 and 23) to both fractions.

Correlation between Diagnostic Tests

Of special interest is the observation that the basophil test gave the highest number of positive results correlating with the clinical status of the patients. Thus, 13 patients with clinical symptoms of wheat flour allergy (rhinitis and/or asthma) gave a positive basophil test; in contrast, 2 patients of this group (10 and 22) gave negative skin and RAST test with wheat flour extract. 5 patients with rhinitis and/or asthma, suspecting wheat flour as allergen, gave, however, negative results with all three test methods. In the 13 positive cases, there is no quantitative correlation between the results of the three tests used (table II). This is in contrast to the results of Norman *et al.* [1973] in patients with ragweed hay fever.

Flour allergy is a common occupational disorder in bakers, and therefore, a sensitive and reliable *in vitro* diagnostic method is of great importance. The basophil test has recently been automatized [Ruff *et al.*, 1967; Straganlan, 1974] and whole blood can be used instead of isolated leukocytes. This method should be explored as a routine diagnostic test in allergic subjects. Skin testing exposes the patient to some discom-

fort and risks and an *in vitro* substitute is highly desirable.

Acknowledgements

Financial support from Arbetarskyddsfonden (Stockholm), Ellen Walter and Lennart Hesselman Foundation for Scientific Research (Stockholm) and Robert Koch Foundation (Bonn) is gratefully acknowledged. We are indebted to Mrs. Kirsten Ebbesen, Mrs. Eva Haardeng-Larsen and Mrs. Iben Hjort for expert technical assistance.

References

- Aas, K. and Belin, L.: Standardization of diagnostic work in allergy. *Acta allerg.* 27: 439-469 (1972).
- Axelsen, N. M.; Krøll, J., and Weeke, B.: A manual of quantitative immunoelectrophoresis. Methods and applications. *Scand. J. Immunol.* 2: suppl. 1 (1973).
- Baagø, K. H.: Mehlidiosynkrasie als Ursache von vasomotorischer Rhinitis und Asthma. *Klin. Wochr.* 1933 I: 792.
- Bazaral, M. G. and Hamburger, R. N.: Standardization and stability of immunoglobulin E (IgE). *J. Allergy clin. Immunol.* 49: 189-191 (1972).
- Besche, A. de: Serologische Untersuchungen über allergische Krankheiten. *Acta path. microbiol. scand.* 6: 115 (1929).
- Bjerrum, O. J.; Ramlau, J.; Clemmesen, I.; Ingild, A., and Bøg-Hansen, T. C.: An artefact in quantitative immunoelectrophoresis of spectra caused by proteolytic activity in antibody preparations. *Scand. J. Immunol.* 4: suppl. 2, pp. 81-88 (1975).
- Bonnevie, P.: Occupational allergy in bakery; in Stenfort-Kroese Occupational allergy, p. 161 (Leiden 1958).
- Bøyum, A.: Separation of leukocytes from blood and bone marrow. *Scand. J. clin. Lab. Invest.* 21: suppl. 97 (1968).
- Caatberg, T. and Sprengsen, C. M.: Allergic examination of bakers and millers. *Acta allerg.* 1: 283 (1948).

Short Communication

Int. Archs Allergy appl. Im

Anaphylactoid Re

D. Harper and G. B. We

Department of Applied Biolo

Abstract. When the blo
anaphylactoid reaction in o
action in the other hindpaw
raised after alloxan pretreat
reaction is inhibited. The re
effects by involving different

Most rats respond to in
traperitoneal injections of
(molecular weight 44,000-1
anaphylactoid reaction co
oedema of the extremities
pruritus. These have been
tor or R rats. A few do not
breeding *Harris et al.* [1963]
ure to an inherited auto
gene, and a pure line of
clinical dextran has been c
are termed non-reactor or
NR rats are relatively more
shock, tourniquet shock,
shock [Ankier *et al.*, 1967],
tamine and 5-hydroxytry
only with difficulty when d
injected.

Freeman and West [11

Received: February 12, 1976.

- Ceska, M.; Ericson, R., and Varga, J. M.: Radioimmunosorbent assay of allergens. *J. Allergy clin. Immunol.* 49: 1-9 (1972).
- Day, R. P.: Basophil leucocyte separation from human peripheral blood: a technique for their isolation in high purity and high yield. *Clin. Allergy* 2: 205-212 (1972).
- Diedrichs, W. und Lübbers, P.: Das Mehl asthma als Berufskrankheit. *Zentralbl. ArbMed. Arb-Schutz* 5: 189 (1955).
- Dishoeck, H. A. E. van and Roux, D. J.: Sensitization to flour. *J. Hyg.* 39: 674 (1939).
- Gadborg, E.: Om melallergi (Thesis in Danish). Christens, Copenhagen 1956 (extensively reviewed by Bonnevie).
- Goldstein, E. D.; Helner, D. C., and Rose, B.: Studies of reagents to alpha-gliadin via patient with wheat hypersensitivity. *J. Allergy* 44: 37-50 (1969).
- Harboe, N. H. G. and Ingild, A.: Immunization, isolation of immunoglobulins, estimation of antibody titre. *Scand. J. Immunol.* 2: suppl. 1, pp. 161-164 (1973).
- Herkhelmer, H.: The skin sensitivity to flour of bakers' apprentices. A final report of a long-term investigation. *Acta allerg.* 28: 42-49 (1973).
- Hoffmann, D. R.: The specificities of human IgE antibodies combining with cereal grain. *Immunochimistry* 12: 535-538 (1975).
- Kallós, P. and Kallós-Deffner, L.: Flour allergy in bakers. 75th Congr. Trade Union of Swedish Food Workers, Stockholm 1971, p. 182.
- Lowry, O. H.; Rosebrough, N. J.; Farr, A. L., and Randall, R. J.: Protein measurement with the folin phenol reagent. *J. biol. Chem.* 193: 265-275 (1951).
- Löwenstein, H.; Markusen, B., and Wecke, B.: Identification of allergens in extract of horse hair and dandruff by means of crossed radioimmuno-electrophoresis. *Int. Archs Allergy appl. Immun.* 51: 38-47 (1976).
- Löwenstein, H.; Nielsen, L., and Wecke, B.: Fractionation of allergen extracts using timothy (*Phleum pratense*) pollen extracts as a model. *Acta allerg.* 29: 418-432 (1974).
- Löwenstein, H. and Wecke, B.: Purification of human IgE and rabbit antihuman IgE. *Scand. J. Immunol.* 4: suppl. 3, pp. 459-466 (1975).
- Marsh, D. G.: Allergens and the genetics of allergy. *Antigens* 3: 271 (1975).
- Nielsen, L.; Löwenstein, H., and Wecke, B.: Quantitative immunoelectrophoresis used in analysis of the antigen in timothy pollen extract. *Acta allerg.* 29: 385-401 (1974).
- Norman, P. S.; Lichtenstein, L. M., and Ishizaka, K.: Diagnostic tests in ragweed hay fever. *J. Allergy clin. Immunol.* 52: 210-224 (1973).
- Pestalozzi, C. und Schnyder, U. W.: Zur Frage der Bäckerrhinits und des Bäckerasthmas. *Schweiz. med. Wschr.* 1955 I: 498.
- Rowe, D. S.: Measurements of concentrations of human serum immunoglobulins. *Clin. exp. Immunol.* 9: 695-697 (1971).
- Ruff, F.; Seindelle, A.; Dutripon, E., and Parrot, J.-L.: Continuous automatic fluorometric evaluation of total blood histamine. *Nature, Lond.* 216: 279-281 (1967).
- Schwartz, M.: Heridity in bronchial asthma; thesis (Munksgaard, Copenhagen 1952).
- Siraganian, R. P.: An automated continuous-flow system for the extraction and fluorometric analysis of histamine. *Analyt. Biochem.* 57: 383-394 (1974).
- Urbach, E. and Gottlieb, P. M.: *Allergy*; 2nd ed., p. 183 (Grune & Stratton, New York 1946).
- Wecke, B.: Crossed immunoelectrophoresis. *Scand. J. Immunol.* 2: suppl. 1; pp. 47-56 (1973).
- Wecke, B. and Löwenstein, H.: Allergens identified in crossed radioimmuno-electrophoresis. *Scand. J. Immunol.* 2: suppl. 1, pp. 149-153 (1973).
- Wecke, B.; Löwenstein, H., and Nielsen, L.: Allergens in timothy pollen identified by crossed-radio-immuno-electrophoresis (CRIE). *Acta allerg.* 29: 402-417 (1974).

Correspondence to: Dr. Bertil Diamant, Department of Pharmacology, 20, Juliane Maries Vej, DK-2100 Copenhagen Ø (Denmark)

Baker's asthma

Studies of the cross-antigenicity between
different cereal grains

G. BLOCK*, K. S. TSE, K. KIJEK, H. CHAN and M. CHAN-YEUNG

*Respiratory Division, Vancouver General Hospital, and the Department of Medicine,
University of British Columbia, Vancouver, Canada*

(Received 25 October 1982; accepted for publication 19 February 1983)

Summary

Specific IgE antibodies were demonstrated in the sera of six bakers with respiratory symptoms of asthma or bronchitis by the radioallergosorbent (RAST) assay. The specificity of the antibodies was found to be directed not only against the common flours (rye, wheat) used in the bakeries but also against triticale, barley, oat, corn and rice in some of the bakers. By using the RAST inhibition tests, cross-antigenicity was shown to exist between different cereal grains. The degree of cross-reactivity closely paralleled their taxonomic relationship and appeared to be in the following order of decreasing closeness: wheat, triticale, rye, barley, oat, rice and corn. The allergenic activity in the rye and wheat extracts was found to be distributed among various fractions of different molecular weights.

Introduction

In a previous article published in the *Journal*, we have presented evidence to indicate that baker's asthma is a form of allergic asthma mediated by IgE antibodies specific for cereal antigens (Block *et al.*, 1983). Although wheat and rye are the more common flours that they work with, bakers often have occupational exposure to flours from other cereal grains as well. It would be of clinical significance, therefore, to determine the extent of allergic sensitization of symptomatic bakers to different cereal flours and the degree of cross-reactivity between individual cereal grains.

Materials and Methods

Sera

As reported earlier, we have studied seven symptomatic bakers in detail and have established that there was a positive correlation between the level of serum IgE

* Dr Block was the recipient of the British Columbia Christmas Seal Fellowship.

Correspondence: Dr Moira Chan-Yeung, 118-2775 Heather Street, Vancouver, B.C., Canada V5Z 3J5.

antibodies specific for cereal antigens, the degree of non-specific bronchial reactivity and an individual baker's bronchial response to inhalation challenge with an extract of cereal flour (Block *et al.*, 1983). The sera from six of the seven symptomatic bakers were used in the present study; unfortunately, an insufficient quantity of serum was collected from one of the seven subjects. The clinical features of these bakers have been described in our previous article (Block *et al.*, 1983). Five had symptoms of asthma and one had bronchitis. Sera collected from another ten asthmatics who had no occupational exposure to flours were used as controls.

Flour extract

Rice flour and whole grains of rye, spring wheat, triticale, barley, oat and corn were bought from a natural food store. Durum wheat was kindly donated by Ogilvie Mills Ltd., Vancouver, B.C. The cereal grains were ground separately to give a fine powder. Individual flour extracts were prepared by stirring a 10% weight/volume (w/v) flour suspension in phosphate-buffered saline (PBS) at 4°C overnight. The solutions were then centrifuged and stored at -20°C.

Fractionation of cereal extracts

Eight mls each of a 10% w/v rye and spring wheat extracts were passed through a Sephadex G100 (Pharmacia Inc., Uppsala, Sweden) column, 2.5 × 90 cm in size. Aliquots of 2.5 ml were collected in each tube. The elution profiles were produced by plotting the absorbance at 280 nm against the eluted volume and are shown in Figs 1 and 2. The molecular weights of the protein peaks in the elution curves were determined by comparison with a calibration graph which was constructed by passing through the same column four standards of known molecular weights, namely, human

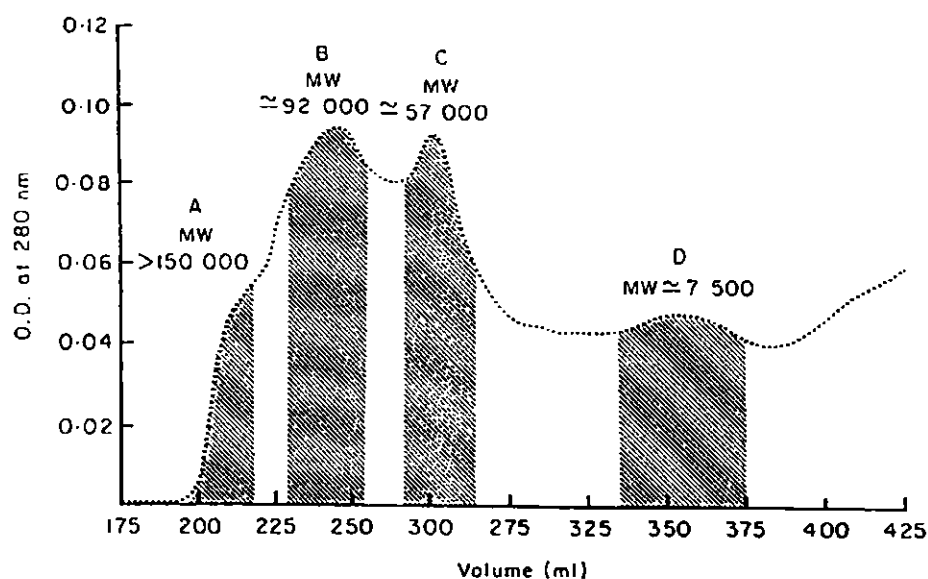


Fig. 1. The elution profile of a 10% w/v rye extract through a Sephadex G-100 column, 2.5 × 90 cm. The shaded areas indicate the volumes pooled for each fraction. The approx. mol. wt for fractions A, B, C, D are 150 000, 92 000, 57 000 and 17 500 daltons, respectively.

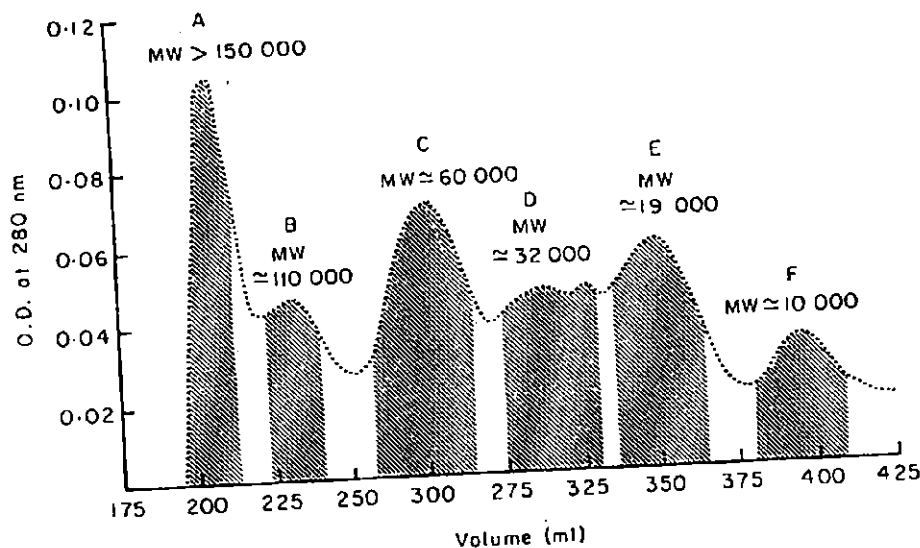


Fig. 2. The elution profile of a 10% w/v spring wheat extract through a Sephadex G-100 column, 2.5/90 cm. The shaded areas indicate the volumes pooled for each fraction. The approx. mol. wt for fractions A, B, C, D, E, F, are 150 000, 110 000, 60 000, 32 000, 19 000 and 10 000 daltons, respectively.

IgG (150 000 daltons), human serum albumin (67 000), chymotrypsinogen (25 000) and ribonuclease (12 500). The protein peaks were designated as A, B, C, D, etc., in decreasing molecular weights. The tubes corresponding to each protein peak were pooled and the eluates concentrated to 2.5 ml which was then kept frozen at -20°C until used. By this method of fractionation, four fractions were obtained from the rye extract and six fractions obtained from the spring wheat extract.

Preparation of allergen discs for RAST

The method of coupling of flour extract to paper discs was modified from the method of Ceska, Erickson & Varga (1972). Briefly, 6-mm-diameter discs were punched out from Whatman 541 filter papers. One hundred washed discs were put in a beaker containing 30 ml of distilled water. After 500 mg of cyanogen bromide was added to the solution, the pH was adjusted to 11.0 for 15 min with 1 N sodium hydroxide. The activated discs were washed in a Buchner funnel with cold distilled water, and then with cold 0.1 M bicarbonate buffer (pH 8.6).

Ten ml of the 10% w/v flour extract was added to the activated discs and mixed overnight at 4°C . The discs were washed five times with cold bicarbonate buffer; 20 ml of 0.5 M ethanolamine in the same buffer was then added to the discs and were mixed at room temperature for 2 hr. The discs were washed once with bicarbonate buffer, once with 0.1 M acetate buffer (pH 4.0), three times with PBS and once with RAST buffer (Pharmacia Inc.). The discs were stored in RAST buffer at 4°C until used.

Radiallergosorbent (RAST) assay

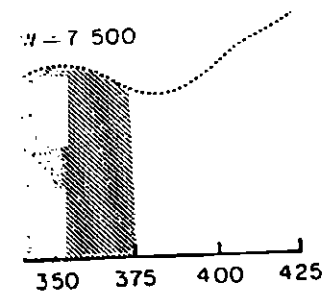
A 0.05 ml serum sample was pipetted in a tube containing an allergen disc. The tubes were shaken on a clinical rotator at room temperature for 3 hr and washed four times with RAST buffer. Then 0.05 ml of ^{125}I -labelled rabbit anti-human IgE (Pharmacia

bronchial reactivity
challenge with an extract of
symptomatic bakers were
serum was collected
have been described
of asthma and one had
no occupational

oat and corn were
decontaminated by Ogilvie Mills
to give a fine powder.
t/volume (w/v) flour
solutions were

passed through a
mm. 2.5 x 90 cm in size.
were produced by
are shown in Figs 1
the elution curves were
constructed by passing
lights, namely, human

W = 7 500



100 column, 2.5 x 90 cm. The
mol. wt for fractions A, B, C, D are

Inc.) was added to each tube and the tubes were again shaken on the rotator at room temperature overnight. The tubes were washed four times with RAST buffer and the radioactivity was measured by a gamma counter. The uptake of radioactivity of the allergen discs was expressed as the RAST value which was the ratio of the radioactivity of the baker's serum sample to that of normal control.

Radioallergosorbent (RAST) inhibition tests

The antigen specificity of the serum RAST activity was determined by the degree of inhibition of serum RAST values by prior absorption of the serum sample with a flour extract. Aliquots of a serum sample in 0.15 ml were mixed with different amounts of a 10% flour extract and left at room temperature for 3 hr. Then 0.05 ml of the sample was used for the RAST assay, using an allergen disc containing the same cereal antigen. The results were expressed as:

$$\% \text{ inhibition} = \frac{(B) - (A)}{(B)} \times 100\%$$

where (B) represents the serum RAST value before incubation with flour extracts and (A) represents the serum RAST value after incubation with flour extracts. Similarly, the antigenicity of the four fractions of the rye flour extract and the six fractions of the wheat flour extract obtained by fractionation through a Sephadex G-100 column was also measured by the ability of each fraction to inhibit the RAST value of a given serum sample.

The degree of cross-reactivity between differential cereal flours was also determined by the RAST inhibition test. In this case, 0.15 ml of the serum sample was pre-incubated with 0.05 ml of the cereal extract to be tested and then the RAST assay was carried out using rye or wheat allergen discs.

Results

Serum RAST values against different cereal flours

These results are shown in Table 1. In comparison with the ten asthmatic controls who had no occupational exposure to flours, each of the six symptomatic bakers was found to have elevated serum RAST values for several of the cereal flours. As reported in our earlier article (Block *et al.*, 1983), four of six symptomatic bakers (bakers 1-4) had positive reactions while the remaining two had negative reactions to antigenic bronchoprovocation with rye or wheat flour extracts. The sera from bakers 1-4 were found to have considerably higher RAST values than the sera from bakers 5 and 6. These subjects not only had elevated serum RAST values for several of the taxonomically closely related cereals such as rye, wheat, durum wheat and triticale (a hybrid species between rye and wheat), but several of them also had very high values for barley (bakers 2, 3, 4), corn (bakers 3, 4), oat (baker 3) and rice (baker 4). The latter four cereal grains have a much more distant taxonomic relationship with rye and wheat. The taxonomic chart of different cereal grains has been published previously by Baldo, Krilis & Wrigley (1980).

Antigenic specificity of the serum RAST activity

The results of the RAST inhibition tests are shown in Fig. 3. Addition of increasing amounts of a particular flour extract to a serum sample from a baker prior to the RAST

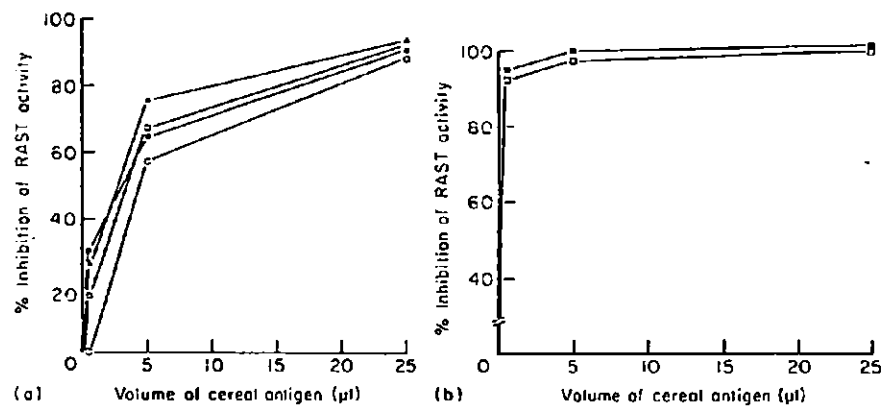


Fig. 3. (a) Antigenic inhibition of serum RAST activity against rye (▲), spring wheat (□), barley (■) and oat (○). Percent inhibition of anti-cereal RAST activity was plotted against the volume of corresponding flour extract pre-incubated with the serum of baker 3 before the RAST assay. (b) Antigenic inhibition of serum RAST activity against corn (■) and rice (□). Percent inhibition of anti-cereal RAST activity was plotted against the volume of the corresponding flour extract pre-incubated with the serum of baker 4 before the RAST assay.

procedure resulted in dose-dependent inhibition of the serum RAST value for the corresponding cereal antigen. This would indicate that the serum RAST activity was indeed cereal antigen-specific because the binding of specific IgE antibodies by the addition of flour antigens to serum lead to a suppression of the specific antibody activity as measured by the RAST.

Cross-reactivity between different cereal antigens

The extent that different flour extracts are able to inhibit the serum RAST activity against rye or wheat could be used as an index of the degree of cross-antigenicity between cereal antigens. The results of the RAST inhibition tests are shown in Table 2, using the sera from the four bakers with particularly high RAST activities for the experiments. The degree of cross-reactivity between the various cereal grains seemed to have a direct correlation with the closeness of their taxonomic relationship. Thus, triticale appeared to cross-react completely with rye in the RAST inhibition tests. This was not unexpected because triticale is a hybrid species between rye and wheat. Wheat

Table 2. Percent inhibition of serum RAST values for rye by absorption with different cereal antigens*

Baker	Rye	Spring wheat	Durum wheat	Triticale	Barley	Oat	Corn	Rice
Rye disc								
1	100	32.3	58.3	100	32.2	54.8	0	0
2	100	100	100	100	81.3	42.3	0.3	0
3	97.0	88.9	92.8	92.2	56.4	30.2	16.1	0
4	100	100	100	100	75.3	45.5	47.9	34.1

* Rye allergen discs were used for the RAST assay.

and barley were also found to have a high degree of cross-reactivity with rye as compared with oat, corn and rice in the RAST inhibition tests. Again, this finding fits well with the fact that wheat and barley are more close to rye taxonomically than oat, corn and rice.

The antigenicity of various fractions of rye and wheat extracts

Results of the RAST inhibition tests using the various fractions of rye and wheat extracts are shown in Tables 3 and 4 and indicate that the lower molecular-weight fractions are relatively more antigenic than the higher molecular weight fractions. Fractions C and D of the rye extract (approx. mol. wt 57 000 and 17 500 daltons,

Table 3. Percent inhibition of serum anti-rye RAST values by prior absorption with different fractions of a rye extract*

Baker	Fractions			
	A	B	C	D
1	28.4	62.5	72.9	88.5
2	6.3	15.0	15.7	80.3
3	16.2	21.4	75.1	19.7
4	4.1	0	15.4	79.3
5	12.7	28.2	73.3	82.4
6	23.6	48.7	68.6	86.7
Mean	15.2	29.3	53.5	72.8

* Rye allergen discs were used for the RAST assay.

Table 4. Percent inhibition of serum anti-wheat RAST values by prior absorption with different fractions of a wheat extract*

Baker	Fractions					
	A	B	C	D	E	F
1	18.8	23.4	53.5	58.1	48.4	25.0
2	0	0	21.2	32.9	48.4	32.4
3	25.1	40.6	40.1	27.1	20.1	7.1
4	3.8	7.9	16.5	33.3	54.3	63.6
5	37.6	37.4	50.1	42.8	84.0	53.7
6	52.6	38.9	78.6	82.8	70.8	51.5
Mean	23.0	24.7	43.3	46.2	54.3	38.9

* Spring wheat allergen discs were used for the RAST assays.

respectively) and fractions D and E of the wheat extract (approx. mol. wt 32 000 and 19 000 daltons, respectively) induced a higher degree of RAST inhibition than other fractions. It was evident, however, that the major antigenic component of the rye and wheat extracts could not be isolated by fractionation through molecular sieving using a Sephadex G-100 column because the results of the RAST inhibition tests clearly showed that the antigenic activity was identifiable throughout the various fractions of the flour extracts.

Discussion

The results of this study have clearly demonstrated the presence of cross-reactivity between different cereal flours. The degree of cross-antigenicity between different cereal grains as determined by the RAST inhibition assay closely parallels their taxonomic relationship. The order of taxonomic relationship in decreasing closeness is as follows: wheat, triticale, rye, barley, oat, rice, corn (Baldo, Krilis & Wrigley, 1980). Closely related species such as wheat, rye and triticale were found to have a very high degree of cross-antigenicity. Even comparing more distantly related species such as rye, barley and oat, the degree of cross-reactivity between them was still remarkable. Our results are in agreement with those of other investigators who also reported the presence of cross-reactivity between rye, wheat, barley and oat (Baldo, Krilis & Wrigley, 1980) as well as between corn and rice (Hoffman, 1975). By employing the method of two-dimensional cross-immunoelectrophoresis between an extract of wheat or rye flour and the corresponding anti-serum raised in rabbits, Blands *et al.* (1976) were able to identify about forty antigenic components (as distinguished by different bands of immunoprecipitates) in the wheat extract and some of the components were partially identical to that in the rye extract. The existence of cross-reactivity between different cereal flours has important clinical implications. It would mean that bakers, once they are sensitized from occupational exposures, are likely to develop allergies to multiple cereal grains. The present study has indeed confirmed this point. We found that symptomatic bakers commonly developed specific IgE antibodies to a wide range of cereal grains (see Table 1). For sensitized bakers to avoid further occupationally induced respiratory symptoms, they would have to quit working in the bakery altogether. Simply changing their work exposure from one type of flour to another would be an ineffective way to manage the problem.

The allergenic activity of rye and wheat does not appear to be confined to a single component but rather it is distributed among various fractions of different molecular weights of the rye and wheat flour extracts (see Tables 3 and 4). In general, the low molecular-weight fractions seem to be more allergenic, with respect to their reactivity with the specific IgE antibodies of allergic bakers. Other investigators have also reported similar results. When the water-soluble proteins of wheat were fractionated into albumin and globulin fractions by salt precipitation, both fractions were reactive with the specific IgE antibodies from subjects with baker's asthma although the albumin fraction was found to have a higher degree of reactivity (Baldo & Wrigley, 1978). Similarly, the allergenicity of rice was also found to be distributed among various fractions of rice proteins (Shibasaki *et al.*, 1979).

References

- BALDO, B.A. & WRIGLEY C.W. (1978) IgE antibodies to wheat flour components. *Clinical Allergy*, **8**, 109.
- BALDO B.A., KRILIS S. & WRIGLEY C.W. (1980) Hypersensitivity to inhaled flour antigens. *Allergy*, **35**, 45.

- BLANDS, J., DIAMANT, B., KALLOS, P., KALLOS-DEFFNER, L. & LOWENSTEIN, H. (1976) Flour allergy in bakers. *International Archives of Allergy and Applied Immunology*, **52**, 392.
- BLOCK, G., TSE, K.S., KUEK, K., CHAN, H. & CHAN-YEUNG, M. (1983) Baker's asthma. Clinical and immunologic studies. *Clinical Allergy*, **13**, 359.
- ČESKA, M., ERICSSON, R. & VARGA, J.M. (1972) Radioimmunosorbent assay of allergens. *Journal of Allergy and Clinical Immunology*, **49**, 1.
- HOFFMAN D.R. (1975) The specificities of human IgE antibodies combining with cereal grains. *Immunochimistry*, **12**, 535.
- SHIBASAKI, M., SUZUKI, S., NEMOTO, H. & KUROUME, T. (1979) Allergenicity and lymphocyte-stimulating property of rice protein. *Journal of Allergy and Clinical Immunology*, **64**, 259.

approx. mol. wt 32 000 and
A inhibition than other
component of the rye and
high-molecular sieving using a
S inhibition tests clearly
out the various fractions of

presence of cross-reactivity
ig icity between different
ss closely parallels their
tip in decreasing closeness is
do Krilis & Wrigley, 1980).
re und to have a very high
n related species such as
them was still remarkable.
at s who also reported the
oat (Baldo, Krilis &
in, 1975). By employing the
between an extract of wheat
ra its, Blands *et al.* (1976)
as distinguished by different
one of the components were
cross-reactivity between
ould mean that bakers,
likely to develop allergies to
fined this point. We found
E antibodies to a wide range
void further occupationally
quit working in the bakery
or type of flour to another

ear to be confined to a single
e ns of different molecular
3 d 4). In general, the low
ith respect to their reactivity
ther investigators have also
s wheat were fractionated
th fractions were reactive
aker's asthma although the
r ctivity (Baldo & Wrigley,
n to be distributed among
l.

By Jean Bourbeau, MD



OCCUPATIONAL ASTHMA: A PATIENT-ORIENTED APPROACH

Occupational asthma is an important health problem as long-term exposure may result in persistent disease even when the patient leaves the offending work environment. Increased awareness among physicians should improve the recognition of this underestimated health problem in Canada.

In the past few years occupational asthma has attracted considerable medical attention. It is now known that the disorder can be caused by a large number of organic and inorganic compounds. As new materials are introduced into industry, the list of compounds will increase. While the development of new investigative techniques has and will continue to assist the diagnosis of this disease, an increased awareness among physicians is still of considerable importance.

PREVALENCE OF OCCUPATIONAL ASTHMA

The overall prevalence of occupational asthma in Canada is unknown. In the last few years, however, there has been an increase in Workers' Com-

pensation Board claims for occupational asthma as compared to the traditional pneumoconioses. The prevalence of occupational asthma seems to vary depending on the industrial agent, exposure, and specific working conditions. As many as 30% of animal handlers, 5% of workers exposed to volatile isocyanate and 4% of workers exposed to western red cedar dust develop asthma. Proper epidemiologic assessment, especially prospective studies, are needed to clarify the extent of the problem in relation to specific agents or the work environment.

DEFINING THE DISEASE

Airway diseases related to the work environment. As recently recommended by the

DR. BOURBEAU is professor of medicine, Université Laval and active staff member, Centre Hospitalier Universitaire du Saint-Sacrement, Quebec, Quebec.

Occupational Asthma

The prevalence of occupational asthma seems to vary depending on the industrial agent, exposure, and specific working conditions.

Proper epidemiologic assessment, especially prospective studies, are needed to clarify the extent of the problem in relation to specific agents or the work environment.

Dr. Jean Bourbeau



Canadian Thoracic Society, the diagnosis of occupational asthma is usually restricted to patients with variable airway narrowing induced by sensitizing agents in the work environment. Other airway diseases, however, can be related to the work environment:

- Byssinosis due to cotton, flax and jute exposure is recognized as work-related and characterized by "Monday symptoms" with improvement during the week;
- Reactive Airways Dysfunction Syndrome (RADS) due to high level exposure of irritating fumes, smoke or gases may be work-related and is characterized by airway hyperactivity of variable duration with or without airway obstruction.

In practice, the distinction

between an occupational exacerbation of pre-existing asthma and the induction of a new state of airway reactivity may be difficult to make, especially in workers with persistent symptoms who have been exposed to the

In practice, the distinction between an occupational exacerbation of pre-existing asthma and the induction of a new state of airway reactivity may be difficult to make.

compound(s) for a long period.

Causes. There are a large number of agents known to cause occupational asthma. The majority have been reported through single case or case series and less often from epidemiologic studies. There are two distinct classes of sub-

stances which provoke occupational asthma (Table 1). One comprises materials of high molecular weight such as animal products, grain, flour, biologic enzymes and crab. The second group includes materials of low molecular weight such as isocyanates, anhydrides from epoxy resins, exotic wood dust, persulfate and henna used in hairdressing products, and certain fluxes from soldering.

Mechanisms and patterns of asthmatic reactions. Different patterns of asthmatic reactions have been documented in the workplace and should be differentiated by the clinician. These are known as immediate, late and dual reaction.

An immediate reaction occurs within minutes of exposure, with recovery within two hours. It is induced by either nonallergic or allergic stimuli. Nonallergic stimuli such as cold air, exercise and nonspecific irritants induce bronchoconstriction through reflex mechanisms in patients who have pre-existing bronchial hyperreactivity. Allergic stimuli in patients with positive immediate wheal reactions are likely mediated by immunoglobulin antibodies (IgE) and may be associated with a late phase reaction. This type of reaction usually is seen

with the high molecular weight compounds.

The late phase asthmatic reaction commonly begins several hours after exposure, with the maximal response between four and eight hours. Recovery is within 24 hours. Late asthmatic reactions when associated with immediate reaction is called dual reaction. Late and dual reactions may be induced by allergic stimuli or by a number of low molecular weight compounds. The exact immunologic mechanisms are not clear although it is now established that late asthmatic reaction is responsible for airway inflammation and thereafter persistent nonspecific bronchial reactivity.

APPROACH TO DIAGNOSIS

The first step for the physician is to confirm the diagnosis of bronchial asthma. The second is to try to establish a relationship between asthma and the work environment.

History and physical examination. The physician's awareness of the possibility of occupational asthma, combined with a careful patient history, should improve the recognition of this underestimated health problem in industrialized countries (Table 2). The patient may present with typical symptoms of asthma immediately after expo-

TABLE 1

CAUSES OF OCCUPATIONAL ASTHMA*

Agent	Industry
<i>Materials of high molecular weight</i>	
Laboratory animals	Laboratory workers
Plants	
Grain dust	Grain handlers
Flour	Bakers, millers
Crab	Fishery worker
<i>Materials of low molecular weight</i>	
Diisocyanates	
Toluene Diisocyanates	Polyurethane, plastics and varnish industries
Hexamethylene Diisocyanates	Automobile spray painting
Anhydrides	
(phthalic acid, trimellitic and tetrachlorophthalic)	Epoxy resins and plastics
Wood dusts	
Western red cedar and exotic woods	Carpentry, construction cabinetmaking and sawmill
Metals	
Platinum	Platinum refinery
Nickel	Metal plating, stainless steel welding
Chromium	Tanning, stainless steel welding
Cobalt and tungsten	Hard metal industry
Fluxes	
Colophony	Electronic industry
Amino ethyl ethanolamine alcohol polypropylene glycol	Aluminum soldering
Drugs	Pharmaceutical, chemist or medical
Other chemicals	
Persulfate and henna	Hairdresser
Urea formaldehyde	Insulation, resin
Freon	Refrigeration

*This table does not represent a complete list of causal agents

Occupational Asthma

TABLE 2

HISTORY*

Episodic symptoms compatible with asthma

Work-related symptoms:

- Present at work, at night or both
- Deterioration throughout the working week
- Improvement over weekends or holidays

Careful occupational history

Atopy is a risk factor for compounds of high molecular weight

* If history is positive, prompt access to a specialized centre is essential

TABLE 3

OBJECTIVE CONFIRMATION

Combination of methods at work and away:

- Daily PEFR (every two hours)
- Nonspecific bronchial provocation test

Specific bronchial provocation test done in a specialized centre

ence of symptoms in a disproportionate number of workers may be important information. Although the knowledge that the patient is exposed to a known occupational sensitizer is of value, the absence of such a substance does not exclude the diagnosis. The patient may not know what he is exposed to; the physician may not recognize a particular agent as a possible sensitizer; or the agent may be new. It is important to recognize atopy as a risk factor for occupational asthma induced by organic and inorganic compounds of high molecular weight.

Skin and serology tests.

The skin test or specific antibodies tests (such as IgE antibodies) may be useful in the identification of the causal agent(s) where high molecular weight compounds are responsible. While positive skin test and presence of IgE antibodies indicate sensitization, it can also occur in exposed workers without asthma, rhinitis or skin allergies.

Lung function test. Asthmatic as well as occupational asthma patients will often have normal lung function tests on a routine office visit. The presence of airway hyperreactivity, therefore, will need to be confirmed by a nonspecific his-

sure to the offending substance. Often, however, initial symptoms are cough without wheezing, chest oppression or symptoms resembling those of a cold. It should be emphasized that many compounds, especially low molecular weight substances, may induce a late asthmatic reaction. The symptoms, therefore, may not be present at work but may be worse after working hours, such as in the evening or at night. Progressive deterioration throughout the working week with improvement of symptoms over weekends and holidays

are also important clues. Long-term exposure may be responsible for the persistence of asthma symptoms. Examination of the patient in the office is unhelpful generally.

The type of work, materials used, the working environment and the presence of symptoms in a disproportionate number of workers may be important.

A careful occupational history is very important. The type of work, materials used, the working environment and the pres-

tamine test or a methacholine bronchial provocation test.

It is necessary to obtain objective confirmation of a relationship between asthma and the work environment (Table 3). It is common practice to have a peak expiratory flow rate (PEFR) recorded by the patient every two hours both at work and at home over a two week period. The demonstration of increased bronchial reactivity on returning to work, together with appropriate changes in PEFR, suggests a relationship between a sensitizing compound and the presence of asthma. Although it is easy to perform, the PEFR has recognized limitations such as when exposure to an agent is intermittent, persistence of asthma even after removal from exposure and potential falsifying of the results by the patient. Bronchial reactivity is nonspecific and may be increased by viral infection, exposure to acetylsalicylic acid (ASA), sulfites, allergens and even certain irritants such as ozone.

Bronchial reactivity may be decreased by the treatment therapy of oral and topical corticosteroids. Specific bronchial provocation tests are often required to complete the investigation and to establish the relationship between a com-

TABLE 4

MANAGEMENT AND TREATMENT

Avoidance of exposure by change of location or change of work
Usual approach with anti-asthma agents:
Beta 2 adrenergic
Inhaled or oral corticosteroids
Theophylline

pound to which the patient is exposed at work and the presence of asthma. These tests should be performed by experienced personnel under the supervision of a specialist in a hospital. Testing is indicated in a situation where occupational asthma is suspected but a specific compound is unrecog-

Treatment with oral and topical corticosteroids may decrease bronchial reactivity.

nized, when an evaluation at work is for any reason difficult, or if there is a need to confirm the diagnosis for medical/legal purposes.

MANAGEMENT AND TREATMENT

The worker who is suspected of having occupational asthma should not resign from his job until a firm diagnosis has been made, or a compensation claim has been decided. If the asthma is disabling, the patient

should be taken off work duties and, where possible, put on sick benefits. A claim may be made to the provincial compensation board for financial loss, disability and, where possible, enrollment in a program for retraining.

When the relationship between asthma and the workplace or a specific agent has been established, the therapeutic approach includes two major steps (Table 4). First, the patient should avoid exposure to the offending substance by changing location of work or the work itself. The use of masks and respirators should be regarded as temporary protection and cannot usually control occupational asthma. It is well known that long-term exposure is associated with persistent asthma. Secondly, the treatment approach regarding anti-asthma agents is the same in occupational compared to non-occupational asthma. Long-term treatment is sometimes

Occupational Asthma

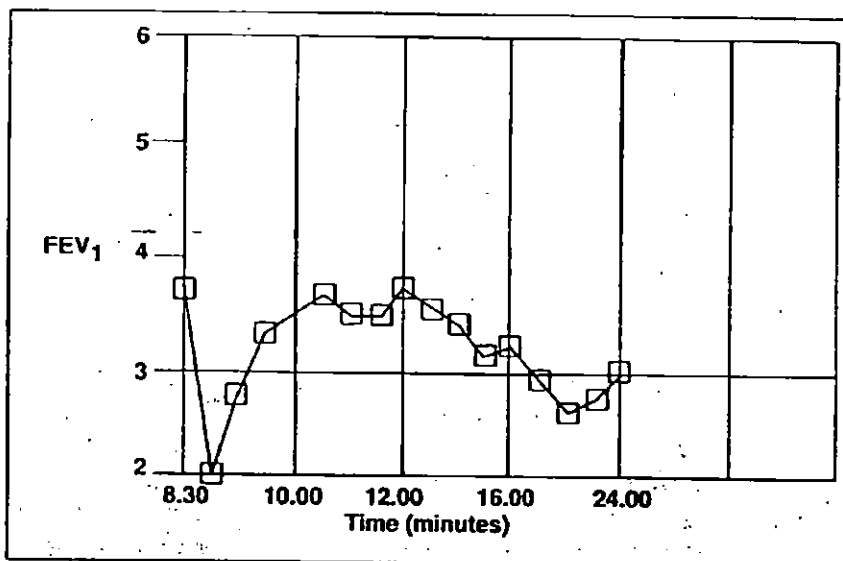


FIGURE 1. Specific bronchial provocation test to flour in a worker presenting dual asthmatic reaction. x = time of exposure; + = 20% drop in FEV₁.

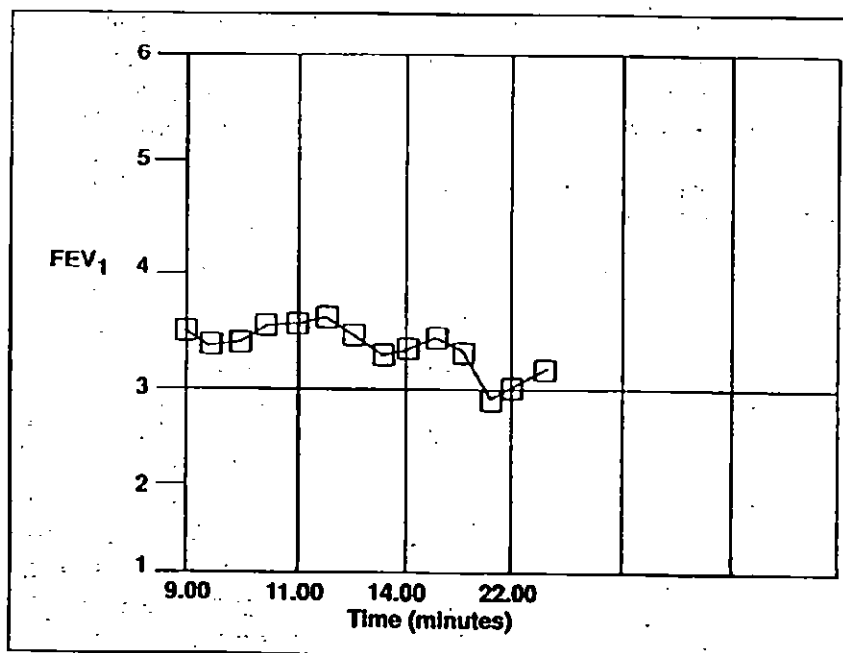


FIGURE 2. Specific bronchial provocation test to stainless steel welding in a worker presenting late asthmatic reaction. x = time of exposure; + = 20% drop in FEV₁.

required in workers with persistent asthma despite their changing work environments.

CASE STUDIES

The following cases illustrate various aspects of the diagnosis of occupational asthma.

Case 1. A 28-year-old male nonsmoker sought help for respiratory symptoms which had progressed in the last few years. His symptoms were characterized by sneezing, cough and dyspnea. They were present following exercise, cold, illness and strong odors. Recently, he had been suffering these symptoms every day and at night. He had been assessed at the local emergency room several times in the last six months. He was using a beta agonist inhaler four to six times a day. His occupational history showed that he had been working for three years in pastry manufacturing. His first symptoms appeared at work as well as at night. Initially, he was free of symptoms during weekends and holidays. His symptoms were then present all week long although they were worse at work.

A past medical history revealed that seasonal rhinitis and asthma were problems from the age of five to 15. His physical examination and the results of baseline lung function tests

were normal. The PEFR showed a major decline at work but also during the weekend. His allergy skin tests were significant for different pollens and flour. A claim to-the-compensation board was made and the patient was referred to a specialized centre.

Analysis. Despite the patient's atopy and past history of rhinitis and asthma, it is still important to exclude the diagnosis of occupational asthma in this case. Further investigation, including a nonspecific histamine bronchial provocation test showed a change in bronchial reactivity. Before exposure to flour, the PC20 was at 2 mg/mL and after exposure the FEV₁ dropped 35% following inhalation of physiologic serum. A specific provocation test with flour showed a dual asthmatic reaction, confirming the diagnosis of occupational asthma (Figure 1).

Case 2. A 35-year-old non-smoking male was seen for coughing spells. His respiratory symptoms began a year previously, specifically during the working week and at night. He was very athletic but had to stop participating in sports because of respiratory symptoms when he exercised.

For the past three years he was employed soldering greasy and sometimes galvanized and

Effective ulcer therapy with a cytoprotective, non-systemic safety profile -

NOTHING WORKS LIKE

NON-SYSTEMIC SULCRATE®

sucralfate/NORDIC



Sulcrate® can 'protect the gastric mucosa against various irritants ... alcohol, ASA, acid...'

Product Monograph,
September 14, 1989



Tablets 1 g
and Suspension
500 mg/5 mL



B.I.D. dosage convenience

FOR PRESCRIBING INFORMATION, PLEASE SEE PAGE 10

Occupational Asthma

stainless steel. Other workers had also complained of respiratory symptoms. The work involved inhaling a significant amount of fumes; the ventilation systems often malfunctioned and he was not using the mask provided by the employer.

The patient's past medical history was non-contributory and the physical examination was unremarkable. His baseline lung function and his PEFR at work and home were normal. He stated, however, that his employer assigned him to do work with low fume exposure during the time he was assessing his PEFR at work. The patient was referred to a specialized centre.

Analysis. Further investigation included a nonspecific histamine bronchial provocation test which shows a PC20 at 16 mg/mL. It was impossible to organize a test at work since the relationship between the worker and his manager was not amicable. A specific provocation test was done in the laboratory in which the worker used the same equipment with different steels on different days. A late asthmatic reaction was shown following stainless steel welding, confirming the diagnosis of occupational asthma (Figure 2).

CONCLUSION

Occupational asthma is under-

diagnosed in Canada. It is an important health problem as long-term exposure may result in persistent asthma despite removal from the work environment. Although recognition of an occupational sensitizer is valuable, the diagnostic approach should involve starting with the symptoms of the patient instead of the specific agent. Definitive objective confirmation of a relationship between asthma and the work environment will often need to be done with specific bronchial provocation tests. Any worker suspected of having occupational asthma should make a claim to the provincial workers' compensation board. If the condition is disabling, the worker should be enrolled for sick benefits. In occupational asthma, treatment is the same as for any asthmatic patient. It is important, however, that the worker avoids exposure by changing the location of the work or the work itself.

SUGGESTED READING

1. Brooks, SM, Weiss, MA, Bernstein, IL: Reactive airways dysfunction syndrome (RADS). Persistent airway hyperreactivity after high level irritant exposure. *Chest* 88:376, 1985.
2. Butcher, BT, O'Neil, CE, Jones, RN: The Respiratory Effects of Cotton Dust—Clinics in Chest Medicine. Salvaggio, JE, Stankus, RP, eds. WB Saunders, Philadelphia, 1983, p.63.
3. Chan-Yeung, M, Lam, S: Occupational asthma. *Am Rev Respir Dis* 133:687, 1986.

THE CANADIAN JOURNAL OF CONTINUING MEDICAL EDUCATION

Publishing schedule
1991

January/February
McMaster University

March
University of British Columbia

April
University of Western Ontario

May
University of Calgary

June/July
Queen's University

August/September
University of Alberta

October
University of Toronto

November/December
McGill University

Occupational Respiratory Diseases Resulting From Exposure to Eggs, Honey, Spices, and Mushrooms

Presented by Carol O'Neil, Ph.D.

More than 200 agents encountered in the workplace have been found to induce occupational asthma and hypersensitivity pneumonitis in susceptible individuals. O'Neil commented that her presentation was intended to be illustrative rather than comprehensive.

Common methods for evaluating allergic reactions include pulmonary function testing, questionnaire administration, both individual and environmental dust level monitoring, skin testing, and radioallergosorbent testing (RAST). Two studies of occupational allergy resulting from inhalation of egg were reviewed. The first study, which involved 25 employees of an egg-processing factory, found occupational asthma in five workers. Positive skin reactivity to one or more egg allergens was found in eight workers, including the five with occupational asthma. The study showed that skin tests are the best clinical predictor of reactivity.

The second study tested 13 bakery workers using an egg and water solution to glaze rolls with a spray gun. While eight of the 13 workers reported symptoms to eggs, there was no consistency of symptoms. Six of 13 subjects were classified as atopic, and two of these were skin test positive to egg (only one of these was symptomatic). Failure to use purified egg fractions may have accounted for the low number of positive skin tests, O'Neil noted. The dose and length of exposure may explain the failure to demonstrate occupational exposure leading to respiratory symptoms. Alternately, the powdered egg or powdered egg yolk may be a more

potent allergen than aerosolized egg. Comparison of subjects in this study, whose main route of administration of egg allergen is inhalation, with 267 subjects whose sole route of administration was ingestion, suggests that egg allergy may be an indicator of a high degree of atopy. Respiratory sensitivity to inhaled egg is not related to the atopic state.

O'Neil presented a case report of a 31-year-old woman who was a breeder of birds. The woman developed respiratory symptoms to birds along with a GI sensitivity to ingested eggs. She showed little reactivity to egg white. In patients with known exposure to birds, it is clinically important to test for allergy to egg yolk as well as to the more common allergen egg white.

There are over 1,600 commercial beekeepers in the United States and 30 companies that process honey on a year-round basis. This number does not include thousands of hobbyists. Cases of occupational asthma have been reported in workers in honey-processing plants. O'Neil presented a case report of a 48-year-old woman who was asymptomatic until her ninth year of employment. Her symptoms were seasonal coughing and wheezing. The subject underwent skin testing, RAST testing, and provocative inhalation challenge. She had no reactivity to honey ingestion and bee stings, and skin test results were negative for common inhalant allergens and honeybee venom. However, skin test and RAST for whole body extracts were positive. After rechallenge using an extract obtained from a personal monitor worn by the patient at work and at home, the allergen was determined to be body parts of honeybees. O'Neil emphasized the importance of challenging non-sensitive asthmatics in order to confirm the specificity of the reaction.

Clinical Immunology Section, Tulane Medical Center

Occupational exposure to garlic may induce asthma in sensitive individuals. Of the five reported cases, two were farm workers who harvested garlic bulbs, and three were workers in a spice factory. Atopy may be an underlying risk factor in garlic sensitivity. O'Neil presented a case report of an electrician employed in a spice factory. After 8 years on the job, he developed severe asthma, and he also noted the immediate onset of wheezing after ingesting garlic. Inhalation challenge showed an immediate reaction; however, ingestion symptoms peaked at 2 hours after challenge.

Unlike occupational asthma, which usually strikes individuals, outbreaks of "mushroom workers' lung," a hypersensitivity pneumonitis, have been reported. Underlying host risk factors remain unknown. Routine clinical immunology laboratory tests are less useful than in the diagnosis of occupational asthma. Antigens derive from two primary sources: microorganisms and mushroom spores. However, workers can be exposed to a variety of antigens, and individual responses vary widely. In a case of 17 workers reporting systemic and respiratory symptoms, there was no common precipitant linking these workers. Occupational asthma has occurred in mushroom growers and soup processors. In growers, the allergen is mushroom spores, while in soup processors, the allergen is dried mushroom powder.

As in the majority of food-handling and -processing industries, prevalence or incidence studies of occupational respiratory diseases are lacking. In some cases, the causative agent may not be the food itself (e.g., poultry mites). The role of atopy is unclear in occupational respiratory diseases. Symptoms of food allergy may also occur in sensitive workers, but this is not universal.

Discussion

Feinberg questioned whether studies had been done on the allergenicity of the polysaccharides and glucosamines in crustacea. Lehrer noted that RAST reactions are due to glycoproteins. High RAST values from the preparations with the water and the meat were a result of proteins. Tests on shell products have not shown any reactivity.

A question from the audience concerned the level of awareness among manufacturers and their responses to the cases and studies that had been discussed. Lehrer said that the two plants in the snowcrab study had made efforts in environmental control, including changes in construction and improved ventilation. In a study of an indoor mushroom-growing plant specializing in shiitake, a species that sporulates throughout its lifecycle, high levels of spores were found, even in the hallways and office areas, according to Lehrer. He added that, while this large company was making serious environmental control efforts, the smaller "mom-and-pop"

operations will be more likely to have occupational allergy problems.

REFERENCES

1. Edwards JH, McConnochie K, Trotman DM, Collins G, Saunders MJ, Latham SM. Allergy to inhaled egg material. *Clin Allergy* 13:427-432, 1983.
2. Bernstein DI, Smith AB, Moller DR, et al. Clinical and immunologic studies among egg-processing workers with occupational asthma. *J Allergy Clin Immunol* 80:791-797, 1987.
3. Reisman RE, Hale R, Wypych JJ. Allergy to honeybee body components: distinction from bee venom sensitivity. *J Allergy Clin Immunol* 71:18-20, 1983.
4. Bousquet J, Dhivert H, Clauzel A-M, Hewitt B, Michel F-B. Occupational allergy to sunflower pollen. *J Allergy Clin Immunol* 75:70-74, 1985.
5. Lybarger JA, Gallagher JS, Pulver DW, Litwin A, Brooks S, Bernstein IL. Occupational asthma induced by inhalation and ingestion of garlic. *J Allergy Clin Immunol* 69:448-454, 1982.
6. van Toorenbergen AW, Dieges PH. Immunoglobulin E antibodies against coriander and other spices. *J Allergy Clin Immunol* 76:477-81, 1985.
7. Jackson E, Welch KMA. Mushroom worker's lung. *Thorax* 25:25-30, 1970.
8. Symington IS, Kerr JW, McLean DA. Type I allergy in mushroom soup processors. *Clin Allergy* 11:43-7, 1981. □

ADDITIONAL REFERENCES

1. Smith AB, Bernstein DI, Aw T-C, et al. Occupational asthma from inhaled egg protein. *Am J Ind Med* 12:205-218, 1987.
2. Lutsky I, Teichtahl H, Bar-Sela S. Occupational asthma due to poultry mites. *J Allergy Clin Immunol* 73:56-60, 1984.
3. Bar-Sela S, Teichtahl H, Lutsky I. Occupational asthma in poultry workers. *J Allergy Clin Immunol* 73:271-275, 1984.
4. Edwards JH, McConnochie K, Davies BH. Skin-test reactivity to egg protein—exposure by inhalation compared with ingestion. *Clin Allergy* 15:147-150, 1985.
5. Hoffman DR, Guenther DM. Occupational allergy to avian proteins presenting as allergy to ingestion of egg yolk. *J Allergy Clin Immunol* 81:484-488, 1988.
6. Paggiaro PL, Loi AM, Toma G. Bronchial asthma and dermatitis due to spiramycin in a chick breeder. *Clin Allergy* 9:571-574, 1979.
7. Bousquet J, Campos J, Michel F-B. Food intolerance to honey. *Allergy* 39:73-75, 1984.
8. Cohen SH, Yunginger JW, Rosenberg N, Fink JN. Acute allergic reaction after composite pollen ingestion. *J Allergy Clin Immunol* 64:270-274, 1979.
9. Ostrom NK, Swanson MC, Agarwal MK, Yunginger JW. Occupational allergy to honeybee-body dust in a honey processing plant. *J Allergy Clin Immunol* 77:736-740, 1986.
10. Falleroni AE, Zeiss CR, Levitz D. Occupational asthma secondary to inhalation of garlic dust. *J Allergy Clin Immunol* 68:156-160, 1981.
11. Couturier P, Bousquet J. Occupational allergy secondary to garlic dust. *J Allergy Clin Immunol* 70:145, 1982.
12. van Toorenbergen AW, Huijskes-Heins MIE, Leijnse B, Dieges PH. Immunoblot analysis of IgE-binding antigens in spices. *Int Arch Allergy Appl Immunol* 86:117-120, 1988.
13. Uragoda CG. Asthma and other symptoms in cinnamon workers. *Br J Ind Med* 41:224-227, 1984.
14. Zuskin E, Skuric Z. Respiratory function in tea workers. *Br J Ind Med* 41:88-93, 1984.
15. Stewart CJ. Mushroom worker's lung—two outbreaks. *Thorax* 29:252-257, 1974. □

Guide de surveillance médicale pour l'asthme professionnel

1- Population cible

- 1.1 Tous les travailleurs(euse) exposé(es) à un des allergènes de la liste (State of Art). Ils s'agit de la liste des substances déjà connues comme aptes à causer de l'asthme en milieu de travail.
- 1.2 La décision d'initier un programme de surveillance appartient au médecin-responsable. En général, un programme devrait être considéré quand la prévalence des réactions asthmatiques chez les exposé(es) dépassent 3% ou quand l'exposition est très élevée.

Exemple 1- Cèdre rouge de l'ouest prévalence 3.4%

- 2- Poussière de grain, prévalence de 2 à 3% mais avec contacts respiratoires fréquents et élevés.

2- Examen pré-embauche ou initial

- ° Information sur les antécédents d'asthme.
Histoire d'exposition professionnelle qui aurait causé de l'asthme.

3- Examen en cours d'emploi

- ° Questionnaire sur l'asthme utilisée par l'Union internationale de la tuberculose (non standardisée). (Voir Guide de surveillance médicale du système respiratoire mai 1987, des DSC).
- ° Si le questionnaire est positif, examen clinique par le médecin responsable ou un médecin désigné.
- ° Si le questionnaire et l'examen clinique orientent vers l'asthme professionnel:
 - ° Compléter par des tests les débits de pointes ou de spirométrie
 - ° Ou/référer à un pneumologue pour diagnostic

* Liste ci-jointe; pp. 689-690



4- Fréquence des examens en cours d'emploi

4.1 Questionnaire respiratoire

- ° Annuel pour deux ans pour les travailleurs nouvellement exposés.
- ° Une première fois pour tous les travailleurs dont l'exposition dépasse deux ans.
- ° Par la suite on encourage l'auto-rapport des symptômes par une information annuelle individuelle ou collective des travailleurs.
- ° Examens cliniques selon les réponses aux questionnaires ou selon les symptômes rapportés.

5- Référence au pneumologue

La consultation se fait au besoin en ayant bien soin d'indiquer qu'on recherche l'asthme professionnel et s'il y a lieu les risques et limitations à l'emploi.

/jp

91-5-3

Occupational Asthma^{1,2}

MOIRA CHAN-YEUNG and STEPHEN LAM

CONTENTS

Historical Perspective
Definition
Causes of Occupational Asthma
Reflex Bronchoconstriction
Inflammatory Bronchoconstriction
Pharmacologic Bronchoconstriction
Allergic Bronchoconstriction
Diagnosis
History
Skin and Serologic Tests
Lung Function Tests
Nonspecific Bronchial Provocation Tests
Specific Bronchial Provocation Tests
Mechanisms of Different Patterns of
Asthmatic Reactions Induced by Bron-
choprovocation Tests
Epidemiologic Studies of Occupational
Asthma
Predisposing Host Factors
Prognosis
Management
Prevention
Summary and Future Research

Historical Perspective

Asthma caused by occupational hazards has been recognized for a long time. In 1713, Ramazzini (1), "father of Industrial Medicine," described grain dust asthma in an article entitled "Diseases of Sifters and Measurers of Grain": "the men who sift and measure are so plagued by this kind of dust that when the work is finished they heap a thousand curses on their calling. The throat, lungs and eyes are keenly aware of serious damage; the throat is choked and dried up with dust, the pulmonary passages become coated with crust formed by dust, and the result is a dry and obstinate cough. The eyes are much inflamed and watery and almost all who make a living by sifting or measuring grain are short of breath and cachectic and rarely reach old age." The term *bysinosis* was first used in 1877 for breathlessness among cotton workers (2). As early as 1911, asthma caused by platinum salt exposure was rec-

ognized among photographic workers (3). However, the interest in occupation as a cause of asthma and hypersensitivity pneumonitis was only revived in the late 1960's, particularly through the work of Pepys in London, England. Since then a number of distinguished researchers have also contributed significantly to our understanding of occupational lung diseases.

Definition

Occupational asthma has been defined as variable airway narrowing causally related to exposure in the working environment to airborne dusts, gases, vapors or fumes (4). Although the definition appears to be straightforward, it is not uniformly accepted, possibly because it is too general. For example, in Britain, the Industrial Injuries Advisory Council defined occupational asthma as "asthma which develops after a variable period of symptomless exposure to a sensitizing agent at work" (5). The Council described only 7 groups of industrial agents: platinum salts, isocyanates, epoxy resins, colophony fumes, proteolytic enzymes, laboratory animals and insects, and grain (or flour) dust. This definition is perhaps too restrictive, and this may have considerable medicolegal implications. Other definitions include agents that induce bronchoconstriction by mechanisms other than sensitization in the working environment as causes of occupational asthma (6-8). This diversity of opinion reflects both the difficulty in defining asthma in general and the fact that there are different pathogenetic mechanisms in occupational asthma.

Causes of Occupational Asthma

Many agents in the working environment can give rise to asthma. In 1980, their number was reported to exceed 200 (4). With the introduction of new materials into the industry and the increased aware-

ness among physicians, the list will grow with time.

Gandevia (6) first introduced the classification of occupational asthma according to pathophysiologic mechanisms: reflex, acute inflammatory, pharmacologic, and immunologic bronchoconstriction. In using such a classification, it should be borne in mind that the mechanism responsible for bronchoconstriction in many instances of occupational asthma is unknown. At times, possibly more than one of the above mechanisms may be involved for the single occupational agent.

Reflex Bronchoconstriction

Cold air, inhalation of inert particles, or noxious gases or fumes cause bronchoconstriction by direct effect on the irritant receptors in the wall (9-12). Reflex bronchoconstriction usually occurs in subjects with pre-existing bronchial asthma rather than in normal healthy subjects. Because the reaction is non-specific and acts as a temporary aggravating factor, it is not often accepted as a cause of occupational asthma.

Inflammatory Bronchoconstriction

In 1970, Gandevia (6) described acute inflammatory bronchoconstriction caused by accidental exposure to high concentrations of irritant gases and vapors such as hydrogen sulphide, diethylene diamine, fume from over-heated plastics, or smoke and fume from combustion of a variety of materials. The air-flow obstruction usually developed within hours, reached a maximum in a week, and stabilized or resolved within 3 to 4 months (13-18).

¹ From the Respiratory Division, Department of Medicine, Vancouver General Hospital, University of British Columbia, Vancouver, British Columbia, Canada.

² Requests for reprints should be addressed to Dr. Moira Chan-Yeung, Department of Medicine, Vancouver General Hospital, 2775 Heather Street, Vancouver, B.C., V5Z 3J5 Canada.

Pathologic studies of patients who died after exposure showed extensive damage and sloughing of the mucosa of the large and small airways along with hemorrhagic pulmonary edema (13). Dense inflammatory cell infiltration, hyperplasia of the bronchial submucosal glands, and terminal bronchiolar fibrosis in addition to destruction of the bronchial epithelium were also observed in one study (19). Lung function studies of patients after acute inhalation injury showed the presence of reversible air-flow obstruction or bronchial hyperreactivity in some patients (14, 15, 20).

In 1981, Brooks and Lockey (21) described "reactive airway disease syndrome" in 13 workers who developed cough, shortness of breath, and wheeze after short, accidental exposures to high levels of irritating fumes, smoke, or gases such as chlorine and ammonia. Typically, the symptoms occurred within hours of initial exposure and generally resolved within several weeks (but they can persist for years after exposure). Nonspecific bronchial hyperreactivity as determined by methacholine challenge test was present in 5 of 6 patients tested. These patients did not have any preexisting respiratory symptoms. In a subsequent study (22), Brooks and coworkers carried out bronchial biopsies on 2 such patients who showed bronchial/bronchiolar epithelial desquamation and mucus cell hyperplasia together with mild infiltration of the bronchial wall by plasma cells and lymphocytes. Changes consistent with bronchial asthma, such as eosinophil infiltration, mucous gland hyperplasia, basement membrane thickening, or smooth muscle hypertrophy were not found in the biopsies. They postulated that the cause of reversible air-flow obstruction and airway hyperreactivity in these patients was due to extensive inflammatory response; subsequent re-epithelialization and probable reinnervation of the bronchial mucosa might have altered the threshold of the receptors. Another possibility for the presence of bronchial hyperreactivity is the increase in epithelial permeability from the inhalation injury (23, 24). Whether "reactive airway disease syndrome" should be used to describe the clinical picture presented by these patients is still uncertain.

Pharmacologic Bronchoconstriction

Some of the agents in the working environment induce asthma by effects similar to those of pharmacologic agonists. In these situations, it is expected that

there should be a dose-response relationship between exposure and response. When the dose is high enough, all exposed subjects are expected to develop bronchoconstriction. There is considerable controversy as to whether these agents, by causing reversible air-flow obstruction, really give rise to "asthma" in the usual sense because they do not give rise to eosinophilia or nonspecific bronchial hyperreactivity.

Byssinosis. Byssinosis occurs in textile workers exposed to dust of cotton, flax, hemp, or jute. The characteristic symptoms are chest tightness, cough, and labored breathing several hours after the patient returns to work on Monday. The symptoms usually disappear overnight, and if they recur on Tuesday, they tend to be milder. Later in the work week the worker usually becomes asymptomatic. The symptoms on Mondays are often associated with a postshift fall in lung function.

The prevalence of byssinosis is higher among workers with the most exposure, such as during ginning, opening, or carding, and lowest in those with the least exposure, such as during slashing or weaving (26-31). The prevalence of byssinosis increases with the duration of exposure. Although byssinosis has been known since 1877, the pathogenetic mechanisms underlying the disease remain unclear. Several nonimmunologic mechanisms have been postulated:

(1) Release of chemical mediators. Cotton dust extracts were found to induce histamine release from isolated human, pig, cow, and sheep lungs but not from the lungs of other species such as rat, mouse, guinea pig, or cat. Cotton dust extracts were also found to contain histamine (32). However, it is thought that the amount of histamine present in cotton dust extracts is too small to induce bronchoconstriction *in vivo* (33). The levels of histamine were found to be elevated in the blood of both cotton and flax workers. Levels were significantly higher on Mondays after the weekend. In asymptomatic workers, the levels of histamine were lower (34). These findings suggest that histamine release is likely to play a role in causing acute bronchoconstriction in these workers. It is quite possible that other chemical mediators, such as prostaglandins or leukotrienes, may be responsible for bronchoconstriction in cotton workers.

(2) Endotoxin. Another popular theory for the mechanism of disease in byssinosis is the presence of endotoxin in cot-

ton dust. Cotton dust is known to be contaminated with bacteria and fungi (35). Rylander and coworkers (36) reported that acute FEV₁ decrements on Monday among cardroom workers correlated better with an exposure index incorporating the number of gram-negative bacteria contaminating bale cotton than with the levels of vertical elutriated cotton dust alone. More recently, Castellan and coworkers (37) found that after 6 h of exposure of human volunteers in the laboratory to cotton dust, the levels of endotoxin in the dust were highly correlated with acute changes in forced expiratory volume in one second (FEV₁).

When endotoxins were given to laboratory animals by aerosol, fever and dyspnea occurred after inhalation. When they were given on 2 consecutive days, the second inhalation had no effect—simulating the "Monday tightness" characteristic of byssinosis (38). The endotoxin was found to activate the complement system (39), with subsequent generation of anaphylotoxins and release of histamine and leukotactic substances. Evidence against endotoxin playing a major role was the finding of Buck and coworkers (40), who demonstrated acute decline in lung function in normal volunteers after exposure to cotton bract extracts even when endotoxin was virtually removed.

Studies of immunologic mechanism in byssinosis have also yielded controversial results. Aqueous extracts of cotton dust have been shown to contain at least 40 separate antigens (41). Dust-specific IgE antibodies were found in the serum of some workers in a cottonseed crushing mill, and a correlation was shown between the presence of specific IgE antibodies and the postshift decline in FEV₁ (42). However, specific IgE antibodies were also found in the serum of 6 of 11 unexposed control subjects. The significance of the dust-specific IgE antibodies has yet to be determined. The fact that most healthy subjects challenged with cotton bract extract demonstrate some degree of bronchoconstriction is against the hypothesis that an immunologic mechanism is present in byssinosis.

Organophosphate insecticide. Acute asthma has been described in farm workers spraying crops with organophosphate insecticides, which act as an anticholinesterase and probably precipitate air-flow obstruction on a pharmacologic basis (43).

Isocyanates and plicatic acid. The pathogenesis of occupational asthma caused by isocyanates and western red ce-

dar (*Thuja plicata*) is still controversial. The role of immunologic mechanisms will be discussed later. The pharmacologic effects of diisocyanate compounds were explored using *in vitro* techniques. Toluene diisocyanate (TDI) was found to compete with isoproterenol-induced production of intracellular cyclic AMP in peripheral blood lymphocytes (44). The effect appears to be dose-dependent (45). This antagonistic property of TDI differs from classic beta-adrenergic blockade because it also affects prostaglandin E₂ (44) and glucagon receptors (46). It should be noted that these properties occurred only in relatively high concentrations of TDI. Moreover, in these *in vitro* experiments, 10% dimethyl sulphoxide was used as the solvent for TDI. Dimethyl sulphoxide may alter the phospholipid mobility and render the membranous receptors more vulnerable to TDI. In reviewing all the recent experimental data, Bernstein (47) concluded that isocyanates probably cause non-specific inhibition of a variety of membrane receptors and enzyme systems, effects that are consistent with the highly reactive properties of these substances.

Plicatic acid, the chemical compound responsible for western red cedar asthma, was found to activate the classic complement pathway with generation of mediators of anaphylaxis (48). However, in both isocyanate- and plicatic-acid-induced asthma, pharmacologic action alone cannot explain why only 5% of the exposed population develop asthma. It is possible that the pharmacologic properties of these compounds may interact and potentiate the immunologic response.

Allergic Bronchoconstriction

By far the greatest number of occupational agents causing asthma have known or suspected allergic properties.

Organic high molecular weight compounds, such as proteins, polysaccharides, glycoproteins, and peptides, can induce allergic response by producing specific IgE antibodies and sometimes specific IgG antibodies. Some of the causes of occupational asthma arising from exposure to animal products, insects, plants, and biological enzymes are shown in table 1. In most instances, positive immediate skin test reactions can be elicited with extracts of the offending agents, and specific IgE antibodies to these antigens can be detected. Atopic subjects are much more frequently affected than nonatopic subjects.

Animal handlers. Recent prevalence studies have shown that asthma occurs in 3 to 30% of workers handling laboratory animals (49-53). The 4 small mammals (rat, mouse, guinea pig, and rabbit) commonly used for laboratory work have all been reported to cause asthma. The major source of allergens was found to be in the proteins in the pelt or urine of these animals; these proteins have a relatively low molecular weight (between 10,000 and 38,000 daltons) (54, 55). There appears to be a considerable cross-reactivity between allergens derived from these animals (55). Rhinitis is commonly present and usually precedes or coincides with the onset of asthma. The symptoms usually occur within a few months after exposure, with the majority appearing within 4 yr. Most studies indicate that atopic subjects are more prone to develop asthma than nonatopic subjects (50-54). Greater than 80% of patients with asthma had positive skin tests to animal antigens (50-53, 55). Specific IgE antibodies were detected (54) but precipitins or specific IgG antibodies were not detected (51, 54).

Grain dust. Grain dust is composed of many materials, including various types of grain and their disintegration products, as well as pollens, fungi, insects, and mites. It also contains silicon dioxide in amounts varying from 5 to 15% of the total dust and is contaminated by excreta of rodents and pigeons. Because of the complex composition of the dust, several clinical syndromes have been attributed to grain dust exposure: asthma, chronic obstructive pulmonary disease, grain fever, and extrinsic allergic alveolitis.

Several studies (67-69) in grain handlers have demonstrated specific bronchial reactions to inhalation challenge with grain dust or grain dust extract. The bronchial reactions usually occurred immediately after challenge; in some workers, the immediate reaction was followed by a late reaction several hours later. Fever, malaise, and leukocytosis sometimes accompanied the late asthmatic reaction (70, 71). Results of investigations into allergic mechanisms in grain-dust-induced bronchoconstriction have been inconclusive. Although Warren and coworkers (67) found good correlation between positive skin reaction to grain dust extract and bronchial reactions, others (68, 69) have failed to do so. Very little information is available as to which are the likely allergens in the grain dust. In 1 case report, recurrent nocturnal asthma was shown to be due to exposure to the grain

mite *Glycyphagus destructor* (59). In another study, durum wheat was found to contain the responsible allergen (69).

Between 4 and 11% of grain workers showed a postshift fall in FEV₁ of greater than 10% (72, 73). The acute effects on lung function were found to be dose-related, the higher the respirable or total dust level, the greater the acute changes in lung function (73, 74). There is now evidence to suggest that the acute reversible changes in lung function from grain dust exposure may be due to nonimmunologic mechanisms. Extracts of grain dust have been shown to activate both the alternative and classic complement pathways *in vitro* (75). More recently, extracts of grain and grain dust were found to induce direct release of histamine from peritoneal mast cells of rats (76). Further studies are required to elucidate the mechanism of grain dust asthma and other clinical syndromes induced by grain dust exposure.

Baker's asthma. For a long time, Baker's asthma was thought to be identical with the asthma experienced by grain workers. It is, however, becoming clear that the 2 conditions are distinct. Most published reports (77, 78) have implicated cereal flours as the responsible allergens for baker's asthma. Affected bakers develop immediate positive skin reactions to extracts of cereal flour, and specific IgE antibodies were found by the radioallergosorbent test (RAST) (78-82). Considerable cross-antigenicity was found between different cereal grains such as wheat, rye, triticale, barley, and oat (79, 83).

There are no prevalence studies of asthma among bakers in Britain or in North America, but there are good studies on flour allergy from the Federal Republic of Germany. Herxheimer (84) skin tested all baker's apprentices in West Berlin and found a progressive increase in the number showing sensitivity to flour, exceeding 20% by the fifth year of apprenticeship. Seven percent developed skin, nasal or bronchial symptoms. A more recent study by Thiel and Ulmer (85) showed allergic symptoms in almost 20% of established bakers; all of them had rhinitis and most had asthma as well. It is interesting to note that each year in West Germany approximately 300 bakers claim industrial injury compensation and approximately a quarter receive it (85).

Biologic enzymes. Shortly after the introduction of proteolytic enzymes of *Bacillus subtilis* in detergent production in the United Kingdom in 1966, Flindt (92)

TABLE 1
CAUSES OF OCCUPATIONAL ASTHMA: ALLERGIC MECHANISM HIGH MOLECULAR WEIGHT COMPOUNDS

Agents	Industries	Reference No.	Subjects (n)	Prevalence (%)	Skin Test*	Specific IgE	Precipitin	Broncho-provocation Test
Animal products, insects, other								
Laboratory animals								
Rats	Laboratory workers	49	1,487	3.1				
Mouse	Veterinarians	50	399	7.5	+			+ (12/12)
Rabbit	Animal handlers	51	179	11.7	+			
Guinea pig		52	130	30.4	+			
		53	146	10.3	+			
		54	5		+	+	-	+ (5/5)
		55	11		+			
Birds								
Pigeon	Pigeon breeders	56	10		+			+ (9/10)
Chicken	Poultry workers	57, 58	14		+	+		+ (1/1)
Budgerigar	Bird fanciers							
Insects								
Grain mite	Grain workers	59	1		+		+	+
Locust	Research laboratory	60	119	26	+	+		
River fly	Power plants along rivers	61	1,284	3.1	+			
Screw worm fly	Flight crews	62	182	70	+			
Cockroach	Laboratory workers	63	10		+			+ (4/10)
Cricket	Field contact	64	1		+	-	-	+
Bee moth	Fish bait breeder	65	18	5.5	+		-	+
Moth and butterfly	Entomologists	66	2		+			
Plants								
Grain dust								
	Grain handlers	67	17		+		+	+ (8/15)
		68	22		-	-	-	+ (6/22)
		69	11		+		+	+ (5/11)
Wheat/rye flour								
	Bakers, millers	77	1		+	+	-	+
		78	2		+		+	+ (2/2)
		79	4		+	+		+ (1/1)
		80	7		+	+		+ (4/7)
		85	31		+	+		+ (22/31)
Buckwheat	Bakers	86	3		+			
Coffee bean	Food processor	87	6		+	+		+
Castor bean	Oil industry	88	5			+		+ (2/3)
Tea	Teaworker	89	1		+			+
Tobacco leaf	Tobacco manufacturing	90	1		+	+		+
Hops (<i>Humulus lupulus</i>)	Brewery chemist	91	1		+			
Biologic enzymes								
<i>B. subtilis</i>								
	Detergent industry	93	3		+	+		+ (3/3)
		94	98	50	+			
		95	38	66	+	+	+	+ (9/10)
Trypsin	Plastic, pharmaceutical	96	14	29	+	+	-	+ (3/4)
Pancreatin	Pharmaceutical	97	5					
Papain	Laboratory	98	1		+	+	+	
	Packaging	99	33	46	+	+	-	+ (8/9)
Pepsin	Pharmaceutical	100	1		+	+		+
Flaviastase	Pharmaceutical	101	3		+	+	+	
Bromelain	Pharmaceutical	102	2		+			+ (2/2)
Fungal amylase	Manufacturing, bakers	103	5		+			
Vegetables								
Gum acacia	Printers	104	2		+			+ (1/1)
Gum tragacanth	Gum manufacturing	105	63	51				
		106	1		+			
Other								
Crab	Crab processing	107	303	16	+			+ (33/57)
Prawn	Prawn processing	108	50	36	+	+	+	+ (2/2)
Hoya	Oyster farm	109	1,413	29	+	+		
Larva of silkworm	Sericulture	110	5,519	0.2	+	+		+ (9/9)

* Skin test to specific antigen.

described an increased prevalence of respiratory disease among exposed workers. In 3 nonatopic workers who had been heavily exposed to these detergent enzymes in the factory (93), immediate and late asthmatic reactions were induced on inhalation provocation testing with enzyme solutions. Since then, asthma among workers in factories producing detergents containing biologic enzymes has been described in other parts of the world

(94, 95). Type I allergic reaction is likely to be responsible for this type of occupational asthma as these enzymes induce an immediate positive skin test in affected patients (94, 95); specific IgE antibodies against these enzymes were demonstrated (95). Sensitization to these enzymes from domestic use of washing powders has not been reported. In the more recent preparations, the enzyme particles are in granulated form, which are less readily inhaled;

as a result, the prevalence of sensitization has been dramatically reduced.

Occupational asthma caused by a number of other biologic enzymes has been described; these include trypsin (96), pancreatin (97), papain (98, 99), pepsin (100), flaviastase (101), and bromelain (102). The prevalence of asthma arising from exposure to these enzymes is unknown, as most of the above studies involved small numbers of workers.

TABLE 2

CAUSES OF OCCUPATIONAL ASTHMA: ALLERGIC OR POSSIBLY ALLERGIC MECHANISM LOW MOLECULAR WEIGHT COMPOUNDS

Agents	Industries	Reference No.	Subjects (n)	Prevalence (%)	Skin Test*	Specific IgE	Precipitin	Broncho-provocation Test
Diisocyanates								
Toluene diisocyanate	Polyurethane Industry plastics, varnish	114	4					+ (4/4)
		117	21	38	-		-	
		118	112	12.5	+		-	+ (5/11)
		119	23	17.4		+		
		120	15		+	-		
		121	26			+		+ (26/26)
		122	17			-		+ (14/17)
		123	195	28	+			+ (12/17)
		128	57	5	-			
		129	1		-	+		
Diphenylmethane diisocyanate	Foundries	132	11			+		+ (6/11)
Hexamethylene diisocyanate	Automobile spray painting	133	1			-	+	+
Anhydrides								
Phthalic anhydride	Epoxy resins, plastics	136	4					+ (3/3)
		137	1		+	+		+
Trimellitic anhydride	Epoxy resins, plastics	138	14	29	+	+		+ (1/1)
		140	14	36		+		
Tetrachlorophthalic anhydride	Epoxy resins, plastics	143	5			-	-	+ (3/3)
Wood dust								
Western red cedar (<i>Thuja plicata</i>)	Carpentry, construction, cabinetmaking, sawmill	144	8					
		145	1,320	3.4	+			
		146	22		+		-	+ (18/22)
		147	185			+		+ (185/185)
California redwood (<i>Sequoia sempervirens</i>)		155	2		-		-	+ (2/2)
Cedar of Lebanon (<i>Cedra libani</i>)		156	8		-		-	
Coccoloba (<i>Dalbergia retusa</i>)		157	2		-			
Iroko (<i>Chlorophora excelsa</i>)		158	1		+		+	+
Oak (<i>Quercus robur</i>)		159	1		-		+	+
Mahogany (<i>Shorea</i> Sp)		159	1		-		+	+
Abrusana (<i>Pouteria</i>)		160	2		+		-	+ (2/2)
African Maple (<i>Triplachiton scleroxylon</i>)		161	2		+	+		+ (2/2)
Tanganyika aninga		162	3		+	-	-	+ (3/3)
Central American Walnut (<i>Juglans olanchana</i>)		163	1		-	-	-	+
Kejaat (<i>Pterocarpus angolensis</i>)		164	1		+			
African zebra wood (<i>Microberlinia</i>)		165	1		+	+	-	+
Metals								
Platinum	Platinum refinery	166	91	57	+			
		167	16		+			+ (10/16)
Nickel	Metal plating	170	1		+		-	+
		171	1		+	-	-	+
		172	1		+	+	+	+
Chromium	Tanning	173	1		-	+		+
		174	1		+			
		175	1		+			
Cobalt	Hard metal industry	177	4		+		+	+ (2/4)
Vanadium		178	12	33				
Tungsten carbide		179	1					
Fluxes								
Aminoethyl ethanolamine	Aluminum soldering	180	3					+ (3/3)
		181	2		-			+ (2/2)
Colophony	Electronic	185	51					+ (34/51)
Drugs								
Penicillins	Pharmaceutical	187	4		-			+ (3/4)
Cephalosporins	Pharmaceutical	188	2		+			+ (2/2)
Phenylglycine acid chloride	Pharmaceutical	189	24	29	+	+		+ (2/2)
Piperazine hydrochloride	Chemist	190	2		+			+ (2/2)
Psyllium	Laxative manufacturer	191	3		+			+ (2/3)
Methyl dopa	Pharmaceutical	192	1		-			+
Spiramycin		193	1		+			+
Salbutamol intermediate		194	1					+
Amprolium HCl	Poultry feed mixer	195	1					+
Tetracycline	Pharmaceutical	196	1					+
Sulphonamide	Manufacturer, brewery	197	12		+			
		198	7		+			
Other Chemicals								
Dimethyl ethanolamine	Spray painting	199	1		-			+
Persulphate salts and henna	Hairdressing	200	2		+			+ (2/2)
Ethylene diamine	Photography	201	1		-			+
Azodicarbonamide	Plastics and rubber	202	151	18.5	-			
Diazonium salt	Photocopying and dye	203	1					+
Hexachlorophene (sterilizing agent)	Hospital staff	204	1					+
Formalin	Hospital staff	205	28	29				+ (2/4)
Formaldehyde	Insulation, resin	206	2		-			+ (2/2)
Freon	Refrigeration	207	1					+
		208	1					+
Paraphenylene diamine	Fur dyeing	209	80	37.5	+			+
Furfuryl alcohol (furan bases resin)	Foundry mold making	210	1					+

* Skin test to specific antigen.

The occurrence of asthma induced by low molecular weight (< 1,000 daltons) inorganic or organic compounds is rapidly increasing (table 2). In some cases, the compound acts as a hapten and combines with protein carrier molecules to act as allergens. Specific IgE antibodies can be demonstrated to the hapten-protein conjugate. It is possible that more than one mechanism may be responsible for the asthmatic reaction caused by many of these agents.

Isocyanates. A number of isocyanates are used in industry: toluene diisocyanates (TDI), diphenyl methane diisocyanate (MDI), hexamethylene diisocyanate (HDI), naphthylene diisocyanate (NDI). The most widely studied of these compounds is TDI. It has been estimated that between 50,000 and 100,000 workers in the United States are exposed to isocyanates. Isocyanates, particularly TDI, are irritants in high concentration; all volunteers exposed to 0.5 ppm experienced irritation of the eyes, nose, and throat (111).

Approximately 5 to 10% of workers exposed to TDI develop asthma (112). The asthmatic symptoms develop in weeks or months after the beginning of exposure. Exposure to very low levels, < 0.005 ppm, may induce an attack of asthma in sensitized patients. The majority of reported cases of TDI-induced asthma have been in nonatopic subjects (113); most have eosinophilia. Inhalation provocation tests with TDI using various methods induce immediate, late, and dual asthmatic reactions in these patients (114, 115).

As asthma can develop after exposure to extremely low concentrations of TDI in sensitized subjects and as only a small proportion of the work force is affected, an allergic reaction involving IgE has been postulated. However, confirmatory evidence is lacking. The presence of homocytotrophic and complement-activating antibodies (116) as well as peripheral blood lymphocyte transformation induced by TDI-protein conjugates (117) have been reported by some investigators. Others have been unable to duplicate their findings (118), and the immunologic mechanism remains unclear.

Because of the complexity of bifunctional isocyanate-protein interactions, Karol and coworkers (119) used a mono-isocyanate, p-tolyl isocyanate (TMI), conjugated to human serum albumin (HSA) as the antigen. They found specific IgE antibodies to this antigen in the serum of 3 of 4 patients sensitized to TDI and not in exposed but nonsensitized sub-

jects. Other investigators, however, found a much lower percentage (0 to 16%) of sensitized patients with specific IgE antibodies to TMI (120-123). It has been suggested recently that the positive RAST in the serum of these patients may in fact be detecting antibodies directed against human serum albumin altered by conjugation with isocyanates (new antigenic determinants) rather than against the specific isocyanate hapten (124).

Chen and Bernstein (125) sensitized guinea pigs parenterally using bifunctional isocyanate conjugated to protein and were able to demonstrate diisocyanate-specific precipitating and IgE antibodies. Further analysis showed that the immune response mounted by these guinea pigs to diisocyanate-protein conjugates was heterogeneous and involved multiple specificities for hapten, carrier protein, and new antigenic determinants. Studies in this area are hampered by the fact that TDI is such a highly reactive chemical; there is no information as to the type of conjugates that might possibly be formed when it is inhaled.

Recent studies by Gallagher and coworkers (120) suggest that perhaps there is a diverse immunoreactivity in patients with TDI-induced asthma. They demonstrated the presence of a specific leukocyte inhibitory factor (LIF) when the peripheral blood leukocytes of patients were challenged with small concentrations of TDI-protein conjugate. Three LIF-positive patients also demonstrated positive intracutaneous reactivity to TDI-HSA. One patient had a markedly positive RAST to TMI-HSA antigen.

It is apparent that further studies are required to clarify the role of immunologic mechanisms in TDI-induced asthma. The heterogeneous immune response should be explored further. Moreover, the use of bifunctional isocyanate as the antigen should be compared with monofunctional isocyanate in human, as well as in animal studies.

Diphenyl methane diisocyanate (MDI) is less volatile than TDI and has been considered to be of low toxicity (126). There are now several reports of asthma and a hypersensitivity pneumonitis related to MDI exposure (127-131). As in TDI asthma, specific IgE antibodies to MDI-protein conjugate were found in only a small proportion of patients (1 of 6) (132). The prevalence of MDI asthma among exposed subjects is unknown. Johnson and coworkers (133) reported a prevalence of 10.3% in a foundry with 78 employees.

Clinical studies with hexamethylene di-

isocyanate (HDI) are even less common (131, 134). Occupational type bronchoprovocation tests have indicated that there may be some cross-reactivity between various isocyanates in the development of asthma (131). Crossed immunologic reactivities between these compounds have been found in a number of studies (123, 124, 135).

Anhydrides. Epoxy resins have many industrial uses including the manufacture of paints, plastics, and adhesives. The acid anhydrides—phthalic anhydride, trimellitic anhydride (TMA), and tetrachlorophthalic anhydride (TCPA)—used in epoxy resin systems cause asthma. Occupational bronchoprovocation tests have confirmed the development of asthmatic reaction after exposure to low concentrations of these fumes or dusts (136). Specific IgE antibodies against phthalic anhydride protein conjugate had been demonstrated in the serum of affected workers (137).

Exposure to trimellitic anhydride can give rise to 4 clinical syndromes: symptoms of airway irritation such as cough, immediate rhinitis and asthma, late asthma with systemic symptoms of fever and malaise, and infiltrative disease in the lung with hemoptysis and anemia (138, 139). Specific IgE antibodies to TMA-protein conjugate have been found in some patients with immediate asthma and rhinitis (138). Specific IgG antibodies were found in those with late asthma or pulmonary disease-anemia syndrome as well as in exposed subjects without symptoms (138, 140). The pathogenesis of late asthma and pulmonary disease-asthma syndrome is not clear.

Animal studies in rabbits and dogs showed that immunization by intrabronchial instillation of TMA induced IgG antibodies to trimellityl-erythrocytes in both types of animals, indicating that the chemical probably reacts with one of the proteins in the airways to form the antigen (141).

In a longitudinal study of 64 workers exposed to trimellitic anhydride between 1977 and 1981, 6 workers had asthma-rhinitis and high levels of IgE antibodies. Five workers developed the late respiratory systemic syndrome, and 1 worker had both syndromes. Removal of the affected workers from exposure led to a decline of the level of antibodies in almost all of them (142).

Wood dusts. A large number of wood dusts are known to give rise to rhinitis and asthma after occupational exposure. The one that has been most extensively studied is western red cedar (*Thuja*

plicata), which is grown in the Pacific Northwest but is exported to other parts of the world such as Australia (144) and Japan (145). Milne and Gandevia (144) first described asthma from western red cedar exposure. Detailed studies by Chan-Yeung and coworkers (146) have shown that the agent responsible for the development of asthma is plicatic acid, which is uniquely present in western red cedar and has a molecular weight of 400 daltons. Inhalation provocation tests in 185 patients with crude extract of red cedar or with plicatic acid induced isolated late asthmatic reaction in 44%, dual reaction in 49%, and isolated immediate asthmatic reaction in 7% (147). The prevalence of a positive skin test against common allergens was 24.7% among these patients, a figure similar to that seen in the general population in British Columbia (147), suggesting that atopic subjects are not unduly prone to develop red cedar asthma. The prevalence of work-related asthma in red cedar sawmill workers is approximately 4% (148). It should be pointed out that the dust concentrations within the sawmills studied were quite low; only 11% of dust samples collected were greater than 1 mg/m³ (149).

Both immunologic and nonimmunologic mechanisms have been implicated. Volatile extracts of western red cedar have been shown to release histamine directly from nonsensitized pig and human lung tissue (150). *In vitro*, plicatic acid was found to activate the classic complement pathway, leading to release of neutrophil chemotactic factors (48). Several clinical features suggest an allergic mechanism: the latent period between onset of exposure and onset of symptoms, development of asthma in only a small proportion of exposed subjects, and the small dose of plicatic acid required to induce a severe attack of asthma. Recently, specific IgE antibodies to plicatic acid-human serum albumin were found in approximately 40% of the patients tested, but specific IgG antibodies were not detected (151). Moreover, in rabbits sensitized with plicatic acid-human serum albumin conjugate, hapten-specific IgE antibodies were detectable by the passive cutaneous anaphylaxis method and specific IgG antibodies were detected by radioimmunoassay, indicating that the plicatic acid protein conjugate is allergenic (152).

It is possible that more than one mechanism may be involved in red cedar asthma. There are a number of volatile compounds present in small quantities

in western red cedar. The tropolones have been shown to act as beta-receptor blockers (153). It is conceivable that the volatile components are released into the air during the process of cutting and kiln drying of the lumber. Plicatic acid is a nonvolatile component and accounts for 50% by weight of all the extractives in red cedar wood and is readily soluble in water (154). In patients with specific IgE antibodies, Type I allergic mechanism is likely to be responsible for the asthmatic reactions.

Metal salts. Complex salts of platinum used in electroplating, platinum refinery operations and in jewelry-making are known to give rise to occupational asthma (166, 167). Pepys and coworkers (167) studied 16 workers with respiratory symptoms from a platinum refinery. Inhalation tests with complex salts of platinum induced immediate asthmatic reaction in 7, late asthmatic reaction in 2, and a dual reaction in 1. The immediate reaction was inhibited by prior treatment with sodium cromoglycate. In all subjects who had immediate asthmatic reaction, prick skin tests using minute concentrations of the complex salt (10^{-4} to 10^{-6} M) produced large wheal and immediate flare skin reaction. Specific IgE antibodies to platinum salts conjugated to human serum albumin were found in sensitized workers by RAST (168). It is interesting to note that hyposensitization has proved useful in preventing symptoms in 1 affected worker (169).

Nickel and chromium are well-known sensitizers and give rise to dermatitis. Moreover, bronchial asthma caused by nickel sulphate has been reported in workers involved in nickel plating (170-172), and asthma caused by chromium has been reported among workers in the manufacture of pigments and in tanning (173-175). A few welders develop asthma when exposed to stainless steel welding but not when exposed to mild steel welding (176). Considerable amounts of chromium and nickel are detected in the fumes released during stainless steel welding but not during mild steel welding. It was thought that chromium or nickel in welding fumes might be the causative agents of asthma in these welders. Other metals such as cobalt (177), vanadium (178), and tungsten carbide (179) were reported to be capable of giving rise to occupational asthma. The mechanisms responsible for these asthmatic reactions are unknown.

Soldering flux. Aluminum solder flux contains aminoethylethanolamine. Ex-

posure to this agent induced isolated late and dual asthmatic reactions in affected workers (180, 181). Colophony, a product of pine tree resin, has been used as a flux since the ninth century. Occupational asthma caused by colophony fumes was first reported in 1976 by Ozhiganova and coworkers (182). Detailed studies were conducted by Burge and coworkers (183-186). In a study of 532 workers in a factory manufacturing consumer electronics (186), occupational asthma was found in 21% of the workers in the high exposure group and in only 4% of the low exposure group. Occupational provocation tests have shown the occurrence of immediate, late, and dual asthmatic reactions after exposure to colophony fumes (185). The mechanism by which colophony induce asthma is unknown. Colophony is an irritant in high concentrations. Many features of colophony asthma suggest an allergic pathogenesis but skin tests and the RAST with extracts of colophony have been negative (184).

Drugs and chemicals. Many drugs and chemicals can give rise to occupational asthma. The mechanisms responsible for these reactions are unknown. They are listed in table 2.

Diagnosis

The diagnosis of occupational asthma is made by confirming the diagnosis of bronchial asthma and by establishing a relationship between the asthma and the work environment.

History

Although a patient with occupational asthma may present with the typical picture of episodic dyspnea, chest tightness, and wheezing associated with air-flow obstruction that is reversible by the administration of a bronchodilator, many patients may initially present with recurrent attacks of "bronchitis" with cough, sputum production, and rhinitis as the predominant symptoms. These symptoms in an otherwise healthy nonsmoker should raise the suspicion that the symptoms may be related to the work environment. It is essential to take a detailed history of the patient's work environment. Careful inquiry is necessary, not only concerning the materials the patient is working with, but also those present in the workplace. It is also useful to find out whether other workers in the same environment develop similar symptoms. The presence of symptoms in a disproportionate number of workers may pro-

vide a clue. The symptoms may be related to particular jobs or introduction of new materials. Patients who develop symptoms immediately after exposure whenever they work with the same material usually recognize the causal relationship. However, it should be emphasized that a large number of substances, particularly low molecular weight compounds, give rise to late asthmatic reactions. The patients often complain initially of cough, chest tightness, and wheeze after working hours in the evenings, and at night, but not during the working hours. Improvement in symptoms over weekends and holidays and recurrence of symptoms on returning to work are also important clues. In the cotton industry, the history of "Monday tightness" is characteristic.

Skin and Serologic Tests

Allergy skin tests with common inhalants and food allergens can be used to define the atopic status of the patient. In some industries, particularly when high molecular weight compounds are responsible for occupational asthma, allergy skin tests with the appropriate extracts may be useful in the identification of the responsible agent. For example, extracts from animal products (50-55), flour (77-82, 85), coffee (87), and castor bean (88) gave immediate positive reactions on skin testing in sensitized subjects.

Specific antibodies such as IgE antibodies may be demonstrated by the RAST or by the enzyme-linked immunosorbent assay (ELISA) to various occupational allergens (54, 57, 60, 79, 80, 85, 87, 88, 90, 98-101, 109, 110). Specific IgE antibodies have also been demonstrated against low molecular weight compounds conjugated to a protein, e.g., plicatic acid (151), phthalic anhydride (137), trimellitic anhydride (140), and isocyanate (121, 123, 124) in a proportion of exposed subjects. It should be borne in mind that positive skin test and presence of specific IgE antibodies indicate sensitization and may occur in exposed workers without asthma, rhinitis, or skin allergies.

Lung Function Tests

At the time of presentation, a patient with occupational asthma may have normal lung function. In patients with red cedar asthma, 80% had a normal FEV₁, and 39% had normal maximal midexpiratory flow rates at the time of diagnosis (211). In patients with normal spirometric measurements, methacholine or his-

mine inhalation tests provide a very sensitive indicator for the presence or absence of current asthma (212).

It is necessary to obtain objective evidence that asthma is work-related. Measurement of lung function before and after a work shift has been used to confirm such a relationship. However, Burge (213) studied preshift and postshift spirometry in 49 electronic workers with asthma from colophony exposure and compared the findings with those from 46 workers without respiratory symptoms who worked in the same part of the factory. Only 22% of the affected workers had a 20% fall in FEV₁ during 1 work shift; similar changes were seen in 11% of the control subjects. He found that the changes in lung function after 1 work shift increased when the patient had been away from work for a period of time, for example, weekends. The shift change in lung function decreased with successive work shifts over the working week, with the patients recovering less each day, and the lung function remained low on the morning of the last day of the working week. Measurement of change in spirometry over 1 work shift, if positive, is good evidence of work-relatedness. It is not a test on which to exclude work-related asthma.

Evidence of an adverse working environment can also be obtained by a "stop-resume" work test during which the patient's daily symptoms, use of medications, and lung function are monitored over a period of time. In addition to measuring the lung function in the laboratory on a single occasion when the patient is away from work and on returning to work, prolonged records of peak expiratory flow rate by the patient at home and at work have been found by Burge (213) to be very useful in establishing the diagnosis of occupational asthma. The patients are asked to make readings every 2 h from waking to sleeping. On each occasion at least 3 readings are made; the best 2 readings should be within 20 L/min of each other. Reproducible readings can usually be obtained using a mini-Wright peak flow meter. The record should be kept for at least a week at work followed by 10 days off work followed by 2 wk at work. The patient should be told to keep the medications the same during this period of monitoring. The mean "daily" peak flow should be plotted with the "daily" maximal and minimal peak flow, with differentiation between days at home and at work. Different patterns of changes in peak ex-

piratory flow rate have been described in occupational asthma (214). The criteria for establishing a positive response has yet to be worked out.

There are limitations to the peak expiratory flow records. If the exposure to the agent causing occupational asthma is intermittent and symptoms can persist for several days after a single exposure, the identification of a specific exposure as the cause of symptoms can be difficult. It is demanding to the worker to perform peak expiratory flow rate every 2 h during his waking hours for a period of 4 to 6 wk. False negative results may be obtained because of concurrent treatment with inhaled corticosteroid or disodium cromoglycate. Moreover, there is the criticism that the worker may falsify the results since he is making the readings himself.

We found a modified approach (214) to be helpful. This includes measurement of peak flow rate 3 times daily (on waking, after work, and before bed) over a period of 3 to 4 wk at work and at home together with serial measurements of nonspecific bronchial reactivity. Measurements of bronchial hyperreactivity assist in providing objective evidence of "sensitization." The demonstration of increase in bronchial reactivity on returning to work and decrease when away from work together with appropriate changes in lung function establishes the causal relationship between symptoms and the work environment (figure 1). To pinpoint the etiologic agent in the working environment responsible for asthma, specific inhalation provocation tests are necessary.

Nonspecific Bronchial Provocation Tests
Measurement of nonspecific bronchial hyperreactivity is usually carried out by histamine or methacholine inhalation test. Two methods are widely used in North America. One is described in detail by Cockcroft and coworkers (215) and the other by Chai and associates (216). Irrespective of the method, it is necessary to standardize the test as described by Hargreave and coworkers (217).

As discussed earlier, methacholine or histamine inhalation tests are useful means of confirming the diagnosis of asthma as well as helping to document that the asthma is caused by "sensitization" to materials at work. Measurement of bronchial hyperreactivity also gives a very good guide as to the initial dose of allergen that one can safely give the patient during bronchial provocation test.

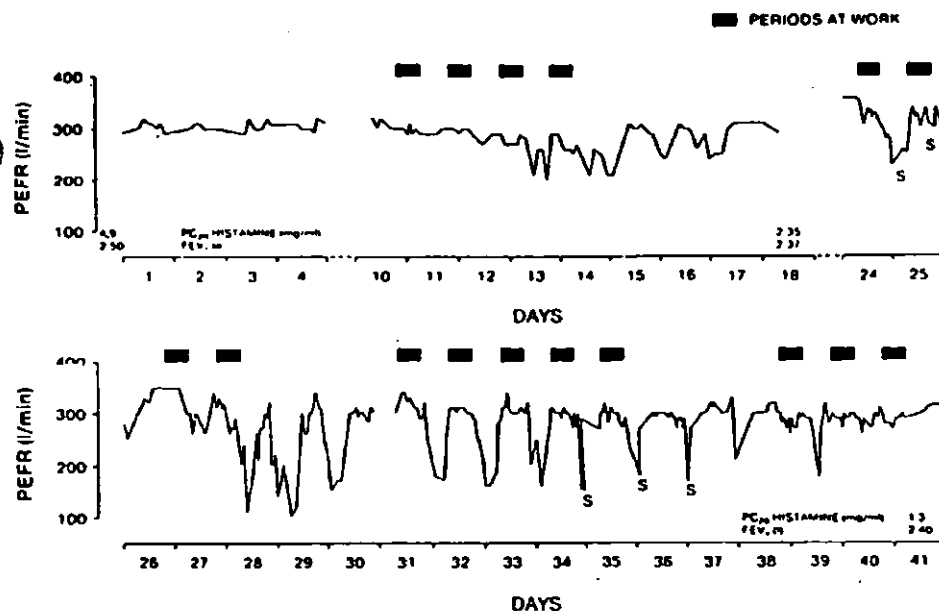


Fig. 1. Prolonged recordings of peak expiratory flow rate (PEFR) and serial measurements of nonspecific bronchial hyperreactivity by histamine challenge tests (PC_{20}) and FEV₁ at work and away from work in a patient with asthma caused by eastern white cedar (*Thuja occidentalis*) (S = use of salbutamol). Note the fall in peak flow rate at the end of the shift during days that the patient was working and the progressive drop in PC_{20} during 3 successive 10-day periods (4.9 mg/ml, 2.35 mg/ml, and 1.3 mg/ml). Reprinted with permission from *J. Allergy Clin Immunol.*

When the allergen is a high molecular weight compound and positive immediate skin reaction is induced by the allergen, the initial dose of allergen to be used for the bronchial provocation test can readily be determined by skin tests with serial dilutions of the allergen. When occupational asthma is due to small molecular weight compounds or when the responsible agent has not been identified, skin tests cannot be done. In patients with red cedar asthma, Lam and coworkers (218) found a good correlation between the severity of reaction to plicatic acid challenge and the degree of nonspecific bronchial reactivity before challenge. For patients with a high degree of nonspecific bronchial hyperreactivity, it is important to start with a small dose of the offending agent for the bronchial provocation test to avoid a severe reaction. Finally, as will be discussed later, measurement of bronchial hyperreactivity may prove to be a useful test to incorporate into the evaluation of disability in patients with persistent asthma after removal from exposure.

Specific Bronchial Provocation Tests

Bronchoprovocation tests with industrial agents are time consuming and not devoid of danger. They should be performed by experienced personnel in a hospital setting where resuscitation facilities are available and where frequent observations can be made. They are in-

dicated in (1) studying previously unrecognized occupational asthma, (2) determining the precise etiologic agent in a complex industrial environment, and (3) confirming the diagnosis for medicolegal purposes.

The methods used in various types of occupational bronchoprovocation tests have been described in detail by Pepys and Hutchcroft (219), and they will not be reviewed here. More sophisticated tests with precise control of exposure levels can be carried out in a whole-body exposure chamber. The chamber enables the levels of exposures to be accurately related to those previously measured in the workplace. It also provides a means of establishing dose-response relationships.

Different patterns of asthmatic reactions occur after bronchial provocation; immediate, late, dual (combined immediate and late), and recurrent nocturnal asthmatic reactions. An immediate asthmatic reaction occurs within a few minutes of challenge, maximal within 10 to 15 min, with recovery within an hour (figure 2). Late asthmatic reactions occur several hours after challenge and are maximal at 5 to 8 h; they usually resolve within 24 h but may persist for a few days (figure 3). More recently, other patterns of asthmatic reaction have been observed: one that develops approximately 1 h after challenge and resolves within 3 to 4 h with another occurring much later, often in the early hours of the fol-

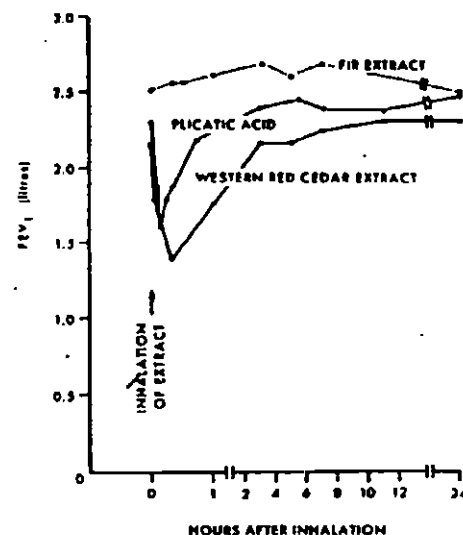


Fig. 2. Immediate asthmatic reaction to western red cedar extract and plicatic acid challenge but no reaction to Douglas fir extract.

lowing morning, and with a tendency to recur at approximately the same time on successive nights after a single exposure. Isolated late asthmatic reactions commonly occur after challenge with industrial materials, particularly low molecular weight compounds. Approximately half of the patients with red cedar asthma develop isolated late asthmatic reactions after an inhalation challenge with plicatic acid (figure 3). Most of the others develop dual asthmatic reactions that consist of an immediate component with spontaneous recovery, followed 4 to 6 h later by the late component. Recurrent nocturnal asthma (figure 4) after a single exposure test has been described with grain dust (59), western red cedar (220), toluene diisocyanate (221), and diphenylmethane diisocyanate (132). Because of the frequent occurrence of late asthmatic

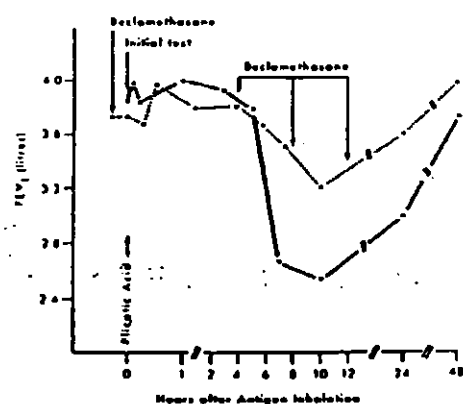


Fig. 3. Late asthmatic reaction to plicatic acid challenge. Administration of beclomethasone before and at intervals after challenge resulted in partial inhibition of the late asthmatic reaction.

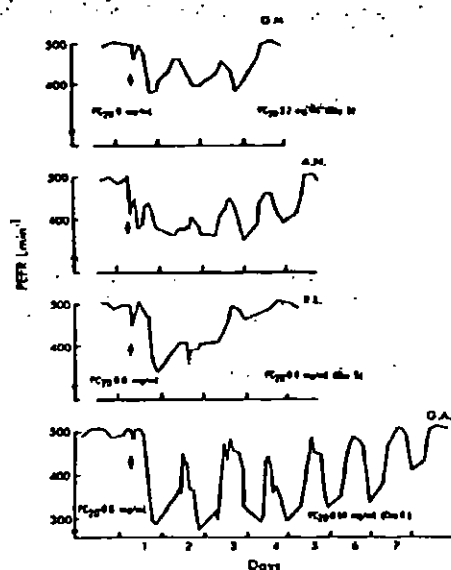


Fig. 4. Recurrent nocturnal asthmatic reaction after a single exposure test to diphenylmethane diisocyanate (MDI) in 4 patients. The shaded area represents 1 A.M. to 8 A.M. The PC_{20} fell from prechallenge level several days after challenge. Arrows indicate time of challenge.

reaction, it is important during inhalation challenge tests to monitor the lung function after inhalation challenge regularly throughout the day and in the evening. Moreover, in any challenge test it is very important to have a control challenge with an appropriate material, for example, the use of other wood dusts in a patient with western red cedar asthma. This is necessary to exclude nonspecific irritant reactions as well as to assess the degree of diurnal variation in lung function in the particular patient. The latter is important in the interpretation of the presence of a late asthmatic reaction.

Certain medications inhibit asthmatic reaction. Disodium cromoglycate inhibits both immediate and late asthmatic reactions, whereas corticosteroids inhibit only the late reaction (219). Bronchodilators should always be withheld before challenge.

Mechanisms of Different Patterns of Asthmatic Reactions Induced by Bronchoprovocation Tests

Bronchoprovocation tests with occupational agents may induce different patterns of asthmatic reactions in the laboratory: immediate, late, and dual asthmatic reactions.

Immediate asthmatic reactions can be induced by nonallergic or allergic stimuli. Nonallergic stimuli induce bronchoconstriction through reflex mechanisms, occurring only in persons with preexisting nonspecific bronchial hyperreactivity.

In patients who have specific IgE antibodies or positive immediate wheal and flare reactions to the responsible agent, the immediate asthmatic reaction is likely to be mediated by IgE reagenic antibodies. Reagenic antibodies have great affinity for membrane receptors of circulating basophils and tissue mast cells, which are the source of potent chemical mediators such as histamine, eosinophilic chemotactic factor of anaphylaxis (ECF-A), neutrophilic chemotactic factor (NCF-A), platelet-activating factor (PAF), and a number of arachidonic acid metabolites such as prostaglandins and leukotrienes (222). The reaction of antigen-reagenic antibodies on the surface of the mast cells lead to a number of enzymatic reactions resulting in the release of the above mediators. Histamine, ECF-A, and NCF-A are present in a preformed state and their release is immediate. The other mediators such as PAF, prostaglandins, and leukotrienes are not released in a preformed state and are synthesized in the cells after antigen-reagenic antibody reaction (222). The release of preformed chemical mediators, chiefly histamine, are responsible for the immediate asthmatic reaction.

Antibodies of the IgG class IgG₄ have been shown to be capable of sensitizing tissue mast cells (223). The sensitizing potential of this antibody is transient and short-term. The significance of this antibody in mediating Type I allergic reaction in humans is unknown.

Late asthmatic reactions occurring as a sequel to an immediate reaction (dual reaction) or in isolation may be induced by allergens or by a number of small molecular weight compounds. It has been postulated that specific IgG antibodies are responsible for late asthmatic reactions (219); however, in most instances of occupational asthma, specific IgG antibodies have not been found. Recently, there has been increasing evidence that the late asthmatic reaction is merely a late-phase allergic reaction mediated by IgE (224, 225). Leukotrienes are synthesized after antigenic challenge and their release is not immediate. This may partly account for the delayed onset of bronchoconstriction. The biologic activity of leukotrienes are more prolonged than is that of histamine. In addition, with release of ECF-A and NCF-A during the IgE-mediated reaction, eosinophils and neutrophils are attracted to the site of the reaction. In a rodent model of late-phase reactions, cellular infiltration (eosinophils and neutrophils) appeared 4 to 6

h after mast cell degranulation and persisted for 24 to 72 h (226). The presence of cellular infiltration during late-phase allergic reaction has also been reported in human cutaneous and nasal studies (227, 228). Recently, in patients with red cedar asthma, leukotriene C₄ (LTC₄), a potent bronchoconstrictor, was recovered in the bronchial lavage fluid after an induced late asthmatic reaction. Furthermore, the severity of the late asthmatic reaction was found to be correlated with the amount of LTC₄ in the lavage fluid (Lam S, Schellenberg R, Chan-Yeung M: unpublished data). The late asthmatic reaction is associated with an inflammatory process that is likely the cause of the nonspecific bronchial reactivity seen in these patients (229, 230). This increase in nonspecific bronchial hyperreactivity is probably responsible for the persistence of asthmatic symptoms in these patients.

Epidemiologic Studies of Occupational Asthma

The majority of the studies in occupational asthma are single case reports, descriptions of a number of cases, and prevalence studies (tables 1 and 2). Long-term prospective studies, which are the most reliable method of investigating the natural history and prognosis, are virtually nonexistent.

The overall prevalence of occupational asthma is unknown. In Japan, it has been estimated that 15% of all adult male asthmatics suffer from asthma caused by occupational exposure (231). In the United States, 2% of all cases of asthma are thought to be of occupational origin (232).

The prevalence of occupational asthma varies depending on the nature of the industrial agent, the concentration of exposure, and the working conditions. For example, in the cotton industry, the prevalence of byssinosis was found to be 25 to 29% in workers exposed to the carding process and 10 to 29% in the spinning process (26). In some villages in Egypt, 90% of all workers exposed to cotton dust develop byssinosis; they are exposed to very high concentrations of dust (233). Approximately 3 to 30% of animal handlers develop asthma because of an allergy to animal protein (49-53, 234). The prevalence of asthma among workers exposed to proteolytic enzymes has been estimated to be between 50 and 66% (94, 95). Approximately 5% of workers exposed to volatile isocyanates develop asthma (235). Similarly, it has

been shown that approximately 4% of workers exposed to western red cedar (*Thuja plicata*) dust have occupational asthma (148). In certain instances, very high percentages of subjects exposed to an occupational inhalant develop asthma. For example, it has been reported that almost every worker in the power plants along the Mississippi River eventually becomes sensitized to river flies (61). Approximately 70% of flight crews dispersing irradiated sterile male screw-worm flies develop allergic symptoms (62). It should be pointed out that any cross-sectional study is likely to underestimate the prevalence of occupational asthma, as affected workers tend to leave the industry.

There are many problems in the identification of asthma. The most important one is the lack of an exact definition of asthma. Most of the epidemiologic studies have relied on subjective evidence for identifying persons with asthma, the most commonly used criteria being affirmative answers to "Have you ever had asthma?" "Was it diagnosed by a doctor?" or to questions about wheezing. Unfortunately, patients and physicians often use the term wheeze as if it were synonymous for asthma. It is well known that wheeze often occurs in patients with chronic bronchitis. The lack of a good asthma questionnaire has hampered studies in the prevalence of asthma. There are a few epidemiologic studies attempting to identify asthma by objective criteria such as documentation of reversible or variable air-flow obstruction or demonstration of nonspecific bronchial hyperreactivity (148, 236, 237). Any test for the demonstration of reversible or variable air-flow obstruction should be simple, standardized, reproducible, easy to perform and safe. Exercise challenge has been used in studies on children successfully (238). Inhalation of histamine or methacholine has been used for identifying bronchial hyperreactivity, and it has been used in several epidemiologic surveys (148, 236, 237) to identify asthma. The test is time-consuming and has yet to be standardized; moreover, there is considerable overlap in the range of bronchial hyperreactivity between asthmatics in remission and normal subjects (230). The results of our own prevalence studies suggest that demonstration of bronchial hyperreactivity does not add more to information derived from questionnaires and simple spirometric measurements (239). Moreover, bronchial hyperreactivity can be found in 11 to 20% of sub-

jects with no respiratory symptoms (239). It is beyond the scope of this review to delve further into the problems of identifying asthma in epidemiologic studies.

Predisposing Host Factors

While environmental factors such as the chemical properties of the agents and the level and duration of exposure are of great importance in the development of occupational asthma, host factors are also important as only a proportion of exposed workers are affected. The knowledge is quite scanty, but a few predisposing host factors appear to be important from the prevalence studies.

(1) *Atopy*. The capacity of certain persons to develop immediate sensitivity after exposure to common environmental allergens, as demonstrated by skin tests or measurements of specific IgE levels, is obviously important. In industries where high molecular weight compounds are the responsible allergens, such as the enzyme detergent industry (240), industries where animals are handled (49, 50), and bakeries (80, 84), atopic workers become sensitized more readily than do nonatopic workers. In industries where low molecular weight compounds are responsible, such as western red cedar mills (147) and isocyanate manufacturers (113), atopy is often not a predisposing factor.

(2) *Smoking*. The role of cigarette smoking in the development of occupational sensitization and asthma is unknown; the findings are often contradictory. Burrows and coworkers (241) observed higher mean levels of total IgE in smokers than in nonsmokers in the general population, and it is possible that smokers' bronchi are more permeable to inhaled agents (242) because of the increase in bronchial epithelial permeability induced by cigarette smoke (243). Increase in epithelial permeability allows greater penetration of antigenic material (244). Among green coffee bean and ispaghul workers, Zetterstrom and coworkers (245) found increased specific IgE levels in smokers. More recently, Venables and colleagues (246), in a study of 300 workers exposed to tetrachlorophthalic anhydride (TCPA), found that 20 of 24 (83.3%) workers with specific IgE antibodies to TCPA-HSA conjugate were current smokers. They also found that there was an interaction between smoking and atopy. The prevalence of antibody was 16.1% in atopic smokers, 11.7% in nonatopic smokers, 8.3% in atopic nonsmokers, and 0% in nonatopic

nonsmokers. It should be pointed out that although smoking may increase the prevalence of sensitization, there is little evidence to suggest that smokers are more predisposed to asthma.

In contrast, among 185 patients with red cedar asthma diagnosed by inhalation provocation tests, 70% were lifelong nonsmokers and only 5% were current smokers, suggesting that nonsmokers are more susceptible (147).

(3) *Nonspecific bronchial hyperreactivity*. The majority of patients with symptomatic occupational asthma had demonstrable nonspecific bronchial hyperreactivity (230). It is unknown at present whether this is the result of occupational exposure or a predisposing factor. Lam and coworkers (230) studied nonspecific bronchial hyperreactivity in 16 patients with red cedar asthma at the time of diagnosis and at intervals after cessation of exposure. As the patients recovered completely, this nonspecific bronchial reactivity decreased and returned towards normal over a period of months. They also demonstrated that nonspecific bronchial reactivity increased after development of late asthmatic reactions induced by inhalation provocation tests in 11 patients. These findings suggest that nonspecific hyperreactivity is a result of exposure rather than a predisposing factor. The only way to ascertain this suggestion is to perform a prospective study of workers and conduct preemployment methacholine or histamine challenge tests with regular follow-up examinations. A study carried out by Zamel and coworkers (247) on healthy nonsmoking twins showed that there was no difference in the slope or threshold response to inhaled methacholine between monozygotic and dizygotic twins. The finding supports the view that environmental factors are more important than genetic factors in determining the variability of acute airway responsiveness to methacholine.

Prognosis

There are now several follow-up studies of patients with occupational asthma. In 1975, Adams (248) found a significant excess of respiratory symptoms in 46 patients with TDI-induced asthma who had not been exposed to TDI for as long as 2 to 11 yr. Moller and coworkers (249) reported that 7 of 12 patients with TDI asthma had persistent asthma even though they were removed from exposure for a mean period of 1.9 years; these patients retained their TDI "sensitivity," as shown by bronchial challenge tests. Pag-

giaro and colleagues (250) studied 27 patients with TDI-induced asthma proved by bronchoprovocation tests 2 yr after their first examination. Eight of 12 patients who left the industry complained of persistent dyspnea and wheeze, and most of them had bronchial hyperreactivity demonstrated by methacholine challenge tests. Continuation of exposure in 15 patients led to further deterioration of air-flow obstruction and increased bronchial reactivity.

Chan-Yeung and coworkers (211), in a follow-up study of 75 patients with red cedar asthma, showed that only half of the patients recovered completely after removal from exposure. The remaining half continued to have recurrent attacks of asthma after a mean period of 3 yr (range 1 to 9 yr) away from exposure. Among the latter group, the severity of symptoms varied considerably from occasional attacks of dyspnea, relieved by the use of aerosol bronchodilators, to persistent chronic asthma that required systemic corticosteroids and other regular medications. Among patients with occupational asthma caused by colophony fumes, Burge (251) demonstrated similar findings. Only 2 of the 20 affected workers who had left exposure were symptom-free on follow-up. However, Burge has pointed out that colophony and pine products are widespread in the home, and the persistent symptoms may have been caused by domestic exposure.

Hudson and coworkers (252) carried out a follow-up study of patients with occupational asthma caused by a variety of agents including small and large molecular compounds. Of the 31 patients with asthma caused by crab processing, 19 were still symptomatic after being away from work for more than 12 months. Of the 32 workers with asthma caused by a variety of agents, such as isocyanate, red cedar, other wood dusts, flour, and antibiotics, only 2 recovered completely after a mean period of 24 months away from exposure.

These studies show that many of the patients with occupational asthma do not recover completely after cessation of exposure even though their condition is frequently improved. The persistence of symptoms is accompanied by the presence of nonspecific bronchial hyperreactivity demonstrated by methacholine or histamine inhalation tests (211, 230, 250, 253). As these patients did not have asthma before they entered the industry, it is fair to assume that their symptoms are the result of occupational exposure.

Exposure to these offending agents altered the reactivity of the airways in these patients by some unknown mechanism.

It could be argued that many workers with occupational asthma were all going to develop late onset asthma and that occupational exposure merely unmasks the predisposition. There are several points against such an argument. First, the prevalence of asthma in industries where occupational asthma is documented is usually higher than that found in the general population. In British Columbia, the prevalence of asthma (from questionnaires) among red cedar sawmill workers was 10.4%; this is significantly higher than the prevalence of asthma found in office workers, 4.3% (148). In some groups of workers exposed to platinum salts and proteolytic enzymes, as many as 50% have developed asthma (166). Second, in patients who recovered from occupational asthma, nonspecific bronchial hyperreactivity returned towards normal (230), indicating that those sensitized acquired a disease from their job. Third, among "intrinsic asthmatics," Brostoff and coworkers (254) found an excess of homozygotes for BW 6 on the HLA-B locus. Such an increase was not found in patients with occupational asthma induced by exposure to colophony fumes (251), suggesting that patients with occupational asthma do not have similar genetic predisposition as "intrinsic asthmatics."

What are the factors that affect the prognosis? In their follow-up study of 75 patients with proved red cedar asthma, Chan-Yeung and coworkers (211) considered various factors, such as duration of exposure before the onset of symptoms, duration of symptoms before diagnosis, age, race, smoking, atopic status, types of asthmatic reaction induced by inhalation challenge, pulmonary function tests, and nonspecific bronchial reactivity at the time of diagnosis. They found that those with persistent asthma had a significantly longer duration of symptoms before diagnosis, lower lung function test results, and a more severe degree of nonspecific bronchial hyperreactivity at the time of diagnosis than did those who recovered. In their follow-up study of patients with occupational asthma caused by a variety of agents, Hudson and coworkers (252) found similar prognostic factors. The findings of these 2 studies suggest that those with persistent asthma after cessation of exposure were diagnosed late and had more severe disease at the time of diagnosis than those

who recovered. Moreover, continuous exposure to TDI in sensitized patients led to further deterioration in lung function and increase in nonspecific bronchial reactivity (250). It is therefore very important that patients with occupational asthma should be diagnosed early and removed from exposure as soon as possible.

Management

When the causal relationship between asthma and the occupational agent has been established, the worker should be removed from exposure. This is often very difficult and requires the cooperation of the employers, the affected worker, the labor union and the Workers' Compensation Board. The employer may attempt to relocate the worker to another area of the plant with no or much less exposure, but unfortunately such "lateral bumping" is not allowed by some labor unions, and the affected worker has to wait until a suitable vacancy occurs. Sometimes even when a transfer is allowed, the worker may have to take a cut in salary and a loss of seniority.

The Workers' Compensation Board should be responsible for ensuring that the working environment is safe by monitoring the levels of exposure at regular intervals, to provide expertise on industrial hygiene, and to ensure that adequate protective devices be given to the affected worker if a transfer to another area of the plant is not possible and the levels of exposure cannot be reduced. When the latter situation arises, the affected worker should use protective devices to minimize exposure, e.g., the use of dust masks and respirators. However, the dust masks are often ineffective because they do not fit well, and compliance is often low when the worker is given a heavy respirator. Considerable research is required to design light, comfortable, and effective respirators. Serial measurement of specific IgE antibodies, if present initially, may be useful for monitoring exposure after preventative measures such as job relocation or the use of respiratory protection (255). It should be emphasized that the use of respirators is for temporary protection and should not be regarded as a method of controlling occupational asthma.

Affected workers who are allowed to continue to work in the same environment should be followed regularly by their physicians. Their lung function and nonspecific bronchial reactivity should be monitored regularly. In addition to the

use of respirators, they may require the use of prophylactic medications such as disodium cromoglycate, beclomethasone dipropionate, and beta-adrenergic agonist. However, at the present time, there is no data to show that prophylactic medications prevent the development of chronic persistent asthma.

Treatment of acute episodes of occupational asthma does not differ from that of any acute attack of asthma. Symptomatic relief of mild attacks is often produced by beta-adrenergic agonists in aerosol form. Xanthine derivatives such as theophylline may be added. In severe and prolonged attacks, systemic corticosteroids may be necessary. Whenever possible, topical steroids such as beclomethasone should be substituted for systemic corticosteroids.

Hyposensitization has been attempted with certain occupational allergens, e.g., complex salts of platinum, which was successful in preventing asthmatic reactions in a chemist (169). Such an approach is not feasible when allergic factors are not involved in the pathogenesis.

Prevention

There are a number of considerations in the prevention of occupational asthma. Efficient environmental control of processes involving sensitization materials is the most important one. It has been documented that the initial development of asthma among workers exposed to TDI is often associated with accidents in which the workers may be exposed to relatively high concentrations of the chemical. Institution of safety measures concerning handling procedures, avoidance of spills, good housekeeping, and education of the workers about these measures are important. There are very few studies relating to the level of exposure to sensitizing materials and subsequent development of occupational asthma. This is the most urgent area requiring research.

Consideration should be given to changes in product formulation whenever possible. For example, in the detergent enzyme industry, encapsulation of the proteolytic enzyme portion of the product reduced the exposure of the workers. Reduction of exposure has dramatically reduced the proportion of workers becoming sensitized in the enzyme detergent industry (256).

Substitution of a harmful material by an innocuous one should be considered. This has not been successful in the use

of MDI in replacing TDI, as MDI also causes occupational asthma (132).

Identification of susceptible workers is another way of preventing occupational asthma. Unfortunately, as discussed earlier, very little is known in this area. Atopy may be an important predisposing factor in occupational asthma caused by high molecular weight compounds but not in occupational asthma caused by low molecular weight compounds. The role of cigarette smoking and nonspecific bronchial hyperreactivity is still uncertain.

Summary and Future Research

More than 200 organic and inorganic compounds are known to cause occupational asthma. With the introduction of new materials into the industry, the list will continue to grow. Although considerable advances have been made in the last 3 decades, especially in the area of diagnosis of occupational asthma, there are considerable gaps in our knowledge that require further investigation.

The prevalence of asthma in various occupational settings is largely unknown. Proper epidemiologic assessment of occupational asthma requires a multidisciplinary approach that combines the efforts of epidemiologists, immunologists, pulmonary physicians, industrial hygienists, chemists, and toxicologists. Moreover, occupational epidemiologic studies require the cooperation of management, labor, and governmental regulatory agencies.

The techniques currently available in identifying subjects with asthma in epidemiologic studies are not satisfactory. There is no validated questionnaire for evaluating asthma or occupational asthma, although such a questionnaire is presently being validated (257). Cross-sectional prevalence studies are likely to underestimate the true prevalence of occupational asthma as workers who develop asthma tend to leave the industry. Prospective studies should be designed to answer the following questions. (1) What is the incidence of occupational asthma in the industry? (2) Is there a dose relationship in sensitization? Can one determine the level of exposure below which no one becomes sensitized? (3) What are the predisposing host factors? (4) Can affected workers return to the same job with reduced levels of exposure without detriment to their health?

The use of methacholine or histamine challenge tests in the field to identify sub-

jects with asthma should be properly assessed. Preliminary data from our studies indicate that it may not add further information to a well-designed questionnaire (239). Whether nonspecific bronchial hyperreactivity is a predisposing host factor in occupational asthma can only be answered by a prospective study with preemployment examination.

The methods used in confirmation of the diagnosis of occupational asthma are also unsatisfactory. Specific provocation tests are time-consuming and not without discomfort to the patients. The use of peak expiratory flow rates 3 to 4 times a day in addition to recording of symptoms and serial measurements of nonspecific bronchial reactivity in establishing the work relationship needs to be studied more vigorously to determine the criteria of positive response and to compare the results with specific bronchial provocation tests. Research should be carried out to develop immunologic means of confirming sensitization to occupational agents.

There is at present a lack of criteria for assessment of functional impairment caused by occupational asthma. The recommendation for evaluation of impairment/disability secondary to respiratory disease is applicable only to patients with pneumoconiosis with a restrictive ventilatory defect such as asbestosis or silicosis or irreversible chronic obstructive lung disease. This set of criteria is inappropriate for a patient with asthma who has variable air-flow obstruction and may have relatively normal lung function while taking a number of medications including systemic corticosteroids. In establishing such criteria, it is important to take into consideration not only lung function but also the degree of nonspecific bronchial hyperreactivity and the amount of medications necessary for the control of asthma even when the patient is no longer exposed to the etiologic agent.

The pathogenetic mechanisms underlying many causes of asthma and occupational asthma are unknown. The mechanism of the late asthmatic reaction and nonspecific bronchial hyperreactivity are not well understood. More direct means of examining the processes that initiate the asthmatic reaction and nonspecific bronchial reactivity are necessary. One approach is the use of bronchial lavage and bronchial biopsy to study the morphologic changes in the bronchial mucosa and submucosa, and the release of

chemical mediators as well as the functional activity of the cells involved in the asthmatic reaction. These methods of study can also be applied to investigate why certain patients with occupational asthma recover, whereas others have persistent symptoms after removal from exposure. Detailed study of these patients will enhance our understanding of the basic mechanism of occupational asthma as well as bronchial asthma in general.

Acknowledgment

The writers wish to thank the Workers' Compensation Board of British Columbia for its continuous support of research in occupational asthma in British Columbia over the years. They also thank Miss Elaine Dorken for her assistance in compiling the tables and references, and Mrs. Ellen Wong and Miss Alice Fong for their secretarial assistance.

References

- Ramazzini B. *De Morbis Artificum Diatriba* (Wright WC, Trans. Disease of workers). Chicago: University of Chicago Press, 1940.
- Proust A. *Traité d'Hygiène, Publique et privée*. Paris: Masson, 1877; 171-4.
- Karasek SR, Karasek M. Preliminary report on the injurious effects of metal platinum, chromates, cyanides, hydrofluoric acid and of material used by silver miners. Report of the Illinois State Commission on Occupational Disease, 1911; 97.
- Newman Taylor AJ. Occupational asthma. *Thorax* 1980; 35:241-5.
- Department of Health and Social Security. Occupational asthma. Report of the Industrial Injuries Advisory Council. London: Her Majesty's Stationery Office, 1981.
- Gandevia B. Occupational asthma I. *Med J Aust* 1970; 2:332-5.
- Murphy RLH Jr. Industrial disease with asthma. In: Weiss EB, Segal MS, eds. *Bronchial asthma: mechanisms and therapeutics*. Boston: Little, Brown, 1976; 517-36.
- Bernstein IL. Occupational asthma in occupational lung disease I. In: Brooks SM, Lockey JG, Harber P, eds. *Clinics in chest medicine*. Vol. 2.2. Philadelphia: W. B. Saunders, 1981; 255-72.
- Horton DJ, Chen WY. Effects of breathing warm humidified air on bronchoconstriction induced by body cooling and by inhalation of methacholine. *Chest* 1979; 75:24-8.
- Widdicombe JT, Kent DC, Nadel JA. Mechanisms of bronchoconstriction during inhalation of dust. *J Appl Physiol* 1962; 17:613-6.
- Frank NR, Amdur MO, Worcester J, Whittenberger JL. Effects of acute controlled exposure to SO₂ on respiratory mechanics in healthy male adults. *J Appl Physiol* 1962; 17:252-8.
- Brooks SM, Mintz S, Weiss E. Changes occurring after freon inhalation. *Am Rev Respir Dis* 1972; 105:640-3.
- Charan NB, Myers CG, Lakshminarayan S, Spencer TM. Pulmonary injuries associated with acute sulphur dioxide inhalation. *Am Rev Respir Dis* 1979; 119:555-60.
- Harkonen H, Nordman H, Korhonen O, Winblad I. Long term effects of exposure to sulphur dioxide lung function four years after a pyrite dust explosion. *Am Rev Respir Dis* 1983; 128:890-3.
- Flury KE, Dines DE, Rodarte JR, Rodgers R. Airway obstruction due to inhalation of ammonia. *Mayo Clin Proc* 1983; 58:389-93.
- Hasan FM, Gchshan A, Fulechan FJD. Resolution of pulmonary dysfunction following acute chlorine exposure. *Arch Environ Health* 1983; 38:76-80.
- Kaufman J, Burkons D. Clinical roentgenologic and physiologic effects of acute chlorine exposure. *Arch Environ Health* 1971; 23:29-34.
- Whitener DR, Whitener LM, Robertson KJ, Baxter CR, Pierce AK. Pulmonary function measurements in patients with thermal injury and smoke inhalation. *Am Rev Respir Dis* 1980; 122:731-9.
- Galea M. Fatal sulfur dioxide inhalation. *Can Med Assoc J* 1964; 91:345.
- Elwood RK, Johnson AJ, Abboud RT, Hung J, Snelling CFT. Pulmonary function and bronchial reactivity in survivors of smoke inhalation (abstract). *Am Rev Respir Dis* 1981; 123(Suppl:A77).
- Brooks SM, Lockey J. Reactive airways dysfunction syndrome (RADS). A newly defined occupational disease (abstract). *Am Rev Respir Dis* 1981; 123(Suppl:A133).
- Brooks SM, Weiss MA, Bernstein IL. Reactive airways dysfunction syndrome (RADS). Persistent airways hyperactivity after high level irritant exposure. *Chest* 1985; 88:376-84.
- Diamond JM. Channels in epithelial cell membranes and junctions. *Fed Proc* 1978; 34:2639-44.
- Simani AS, Inoue S, Hogg JC. Penetration of the respiratory epithelium of guinea pigs following exposure to cigarette smoke. *Lab Invest* 1974; 31:75-81.
- Boushey HA, Holtzman MJ, Sheller JR, Nadel JA. Bronchial hyperactivity (State of Art). *Am Rev Respir Dis* 1980; 121:389-414.
- Zuskin E, Wolfson RL, Harpel G, Welborn JW, Bouhuys A. Byssinosis in carding and spinning workers. *Arch Environ Health* 1969; 19:666-75.
- Fox JJ, Tombleson JBL, Watt A, Wilkie AG. A survey of respiratory disease in cotton operatives. Part I. Symptoms and ventilation test results. *Br J Ind Med* 1973; 30:42-8.
- Fox JJ, Tombleson JBL, Watt A, Wilkie AG. A survey of respiratory disease in cotton operatives. Part II. Symptoms, dust estimations and the effect of smoking habit. *Br J Ind Med* 1973; 30:48-53.
- Imbus HR, Suh MW. Byssinosis. A study of 10,133 textile workers. *Arch Environ Health* 1973; 26:183-91.
- Jones RN, Diem JE, Glindmeyer H, et al. Mill effect and dose-response relationships in byssinosis. *Br J Ind Med* 1979; 36:305-13.
- Merchant JA, Lumsden JC, Kilburn KH, et al. Dose response studies in cotton textile workers. *J Occup Med* 1973; 15:222-30.
- Butcher BT, O'Neil CE, Jones RN. The respiratory effects of cotton dust. In: Salvaggio JE, Stankus RP, eds. *Clinics in chest medicine*. Vol. 4.1. Philadelphia: W. B. Saunders, 1983; 63-70.
- Edwards J. International conference on byssinosis. Mechanisms of disease induction. *Chest* 1981; 79(Suppl:38-43).
- Noweir MH. Highlights of broad-spectrum industrial-hygiene research activities in a developing country—Egypt. *Am Ind Hyg Assoc J* 1979; 40:839-59.
- Prindle B. The microbiology of textile fibers (cotton). *Textile Res* 1934; 5:11-5.
- Rylander RK, Imbus HR, Suh MW. Bacterial contamination of cotton as an indicator of respiratory effects among cardroom workers. *Br J Ind Med* 1979; 36:299-304.
- Castellan RM, Olenchock SA, Hankinson JL, et al. Acute bronchoconstriction induced by cotton dust: dose-related response to endotoxin and other dust factors. *Ann Intern Med* 1984; 101:157-63.
- Pernis B, Vigliani EC, Cavagna C, Finulli M. The role of bacterial endotoxins in occupational diseases caused by inhaling vegetable dusts. *Br J Ind Med* 1961; 18:120-9.
- Wilson MR, Sekul A, Ory R, Salvaggio JE, Lehrer SB. Activation of the alternative complement pathway by extracts of cotton dust. *Clin Allergy* 1980; 10:303-8.
- Buck MG, Schachter EN, Wall JH. Partial composition of a low molecular weight cotton bract extract which induces acute airway constriction in humans. In: Wakekyn PE, ed. *Proceedings of the Sixth Cotton Dust Research Conference*. Memphis, TN: National Cotton Council, 1982; 19-23.
- O'Neil CE, Butcher BT, Hughes JM. Studies of total and specific antibodies in workers employed in cottonseed crushing mills. In: Wakekyn PJ, ed. *Proceedings of the Fifth Cotton Dust Research Conference*. Memphis, TN: National Cotton Council, 1981; 3-6.
- Jones RN, Butcher BT, Hammand YY, et al. Interaction of atopy and exposure to cotton dust in the bronchodilator response. *Br J Ind Med* 1980; 37:141-6.
- Weiner A. Bronchial asthma due to organic phosphate insecticide. *Ann Allergy* 1961; 19:397-401.
- Davies RJ, Butcher BT, O'Neil CE, Salvaggio JE. The *in vitro* effect of toluene diisocyanate on lymphocyte cyclic adenosine monophosphate production by isoproterenol, prostaglandin and histamine. A possible mode of action. *J Allergy Clin Immunol* 1977; 60:223-9.
- Butcher BT, Salvaggio JE, O'Neil CE, Weill H, Garg O. Toluene diisocyanate pulmonary disease. Immunopharmacologic and Mecholy challenge studies. *J Allergy Clin Immunol* 1977; 59:223-7.
- VanErt M, Battigeli C. Mechanism of respiratory injury by TDI (toluene diisocyanate). *Ann Allergy* 1975; 35:142-7.
- Bernstein IL. Isocyanate-induced pulmonary disease: a current perspective. *J Allergy Clin Immunol* 1982; 70(Suppl:24-31).
- Chan-Yeung M, Giclas P, Henson P. Activation of the complement by plicatic acid: the chemical compound responsible for asthma due to western red cedar (*Thuja plicata*). *J Allergy Clin Immunol* 1980; 65:333-7.
- Davies GE, McArdle LA. Allergy to laboratory animals: a survey by questionnaire. *Int Arch Allergy Appl Immunol* 1981; 64:302-7.
- Gross NJ. Allergy to laboratory animals: epidemiologic, clinical, and physiologic aspects and a trial of cromolyn in its management. *J Allergy Clin Immunol* 1980; 66:158-65.
- Cockcroft A, Edwards J, McCarthy P, Anderson N. Allergy in laboratory animal workers. *Lancet* 1981; 1:827-30.
- Hook WA, Powers K, Siraganian RP. Skin tests, blood leukocytes, histamine release of patients

- with allergies to laboratory animals. *J Allergy Clin Immunol* 1984; 73:457-65.
53. Slovak AJM, Hill RN. Laboratory animal allergy: a clinical survey of an exposed population. *Br J Ind Med* 1981; 38:38-41.
 54. Newman Taylor AJ, Longbottom JL, Pepys J. Respiratory allergy to urine proteins of rats and mice. *Lancet* 1977; 2:847-9.
 55. Ohman JL Jr, Lowell FC, Bloch KJ. Allergens of mammalian origin. II: Characterization of allergens extracted from rats, mouse, guinea pig, rabbit pelts. *J Allergy Clin Immunol* 1975; 55:16-24.
 56. Hargreave FE, Pepys J. Allergic respiratory reactions in bird-fanciers, provoked by allergen inhalation provocation tests. *J Allergy Clin Immunol* 1972; 50:157-73.
 57. Bar-Sela S, Teichtahl H, Lutsky I. Occupational asthma in poultry workers. *J Allergy Clin Immunol* 1984; 73:271-5.
 58. Lutsky I, Teichtahl H, Bar-Sela S. Occupational asthma due to poultry mites. *J Allergy Clin Immunol* 1984; 73:56-60.
 59. Davies RJ, Green M, McSchofield NM. Recurrent nocturnal asthma after exposure to grain dust. *Am Rev Respir Dis* 1976; 114:1011-9.
 60. Burge PS, Edge G, O'Brien M, Harries MG, Hawkins R, Pepys J. Occupational asthma in a research centre breeding locusts. *Clin Allergy* 1980; 10:355-63.
 61. Figley KD. Mayfly (*Ephemera*) hypersensitivity. *J Allergy* 1940; 11:376-87.
 62. Gibbons HL, Dille JR, Cowley RG. Inhalant allergy to sawtooth fly. *Arch Environ Health* 1965; 10:424-30.
 63. Berntson HS, McMahon TF, Brown H. Cockroach asthma. *Br J Dis Chest* 1972; 66:61-6.
 64. Harfi HA. Immediate hypersensitivity to cricket. *Ann Allergy* 1980; 44:162-3.
 65. Stevenson DD, Mathews KP. Occupational asthma following inhalation of moth particles. *J Allergy* 1967; 39:274-83.
 66. Randolph H. Allergic response to dust of insect origin. *JAMA* 1934; 103:560-2.
 67. Warren P, Cherniack RM, Tse KS. Hypersensitivity reactions in grain dust. *J Allergy Clin Immunol* 1974; 53:139-49.
 68. Chan-Yeung M, Wong R, MacLean L. Respiratory abnormalities among grain elevator workers. *Chest* 1979; 72:461-7.
 69. doPico GA, Jacobs S, Flaherty D, Rankin J. Pulmonary reaction to durum wheat; a constituent of grain dust. *Chest* 1982; 81:55-61.
 70. Tse KS, Warren P, Janusz M, McCarthy DS, Cherniack RM. Respiratory abnormalities in workers exposed to grain dust. *Arch Environ Health* 1973; 27:74-7.
 71. doPico GA, Flaherty D, Bhansali P, Chavaje N. Grain fever syndrome induced by airborne grain dust. *J Allergy Clin Immunol* 1982; 69:435-42.
 72. Chan-Yeung M, Schulzer M, MacLean L, Dorken E, Grzybowski S. Epidemiologic health survey of grain elevator workers in British Columbia. *Am Rev Respir Dis* 1980; 121:329-37.
 73. doPico GA, Reddan W, Anderson S, Flaherty D, Smalley E. Acute effects of grain dust exposure during a work shift. *Am Rev Respir Dis* 1983; 128:399-404.
 74. Corey P, Hutcheon M, Broder I, Mintz S. Grain elevator workers show work-related pulmonary function change and dose effect relationships with dust exposure. *Br J Ind Med* 1982; 39:330-7.
 75. Olenchock SA, Mull JC, Major P. Extracts of airborne grain dust activate alternative and classical complement pathways. *Ann Allergy* 1980; 44:23-8.
 76. Warren P, Holford-Strevens V. Induction of histamine release in vitro from rat peritoneal mast cells by extracts of grain and grain dust. Presented in the New Orleans Conference on Agricultural Dusts 1984.
 77. Wilbur RD, Ward GW. Immunological studies in a case of baker's asthma. *J Allergy Clin Immunol* 1976; 58:366-72.
 78. Hendrick DJ, Davies RJ, Pepys J. Baker's asthma. *Clin Allergy* 1976; 6:241-50.
 79. Baldo BA, Krilis S, Wrigley CW. Hypersensitivity to inhaled flour allergens. *Allergy* 1980; 35:45-56.
 80. Block G, Tse KS, Kijek K, Chan H, Chan-Yeung M. Baker's asthma: clinical and immunological studies. *Clin Allergy* 1983; 13:359-70.
 81. Blands J, Diamant B, Kallos P, Kallos-Deffner L, Lowenstein H. Flour allergy in bakers. *Int Arch Allergy Appl Immunol* 1976; 52:392-409.
 82. Bjorksten F, Backman A, Jarvinen K, et al. IgE specific to wheat and rye flour protein. *Clin Allergy* 1977; 7:473-83.
 83. Block G, Tse KS, Kijek K, Chan H, Chan-Yeung M. Baker's asthma: studies of cross-antigenicity between different cereal grains. *Clin Allergy* 1984; 14:177-85.
 84. Herxheimer H. The skin sensitivity to flour of bakers' apprentices. *Acta Allergol* 1973; 28:42-9.
 85. Thiel H, Ulmer WNT. Baker's asthma: development and possibility of treatment. *Chest* 1980; 78(Suppl:400-5).
 86. Ordman D. Buckwheat allergy. *S Afr Med J* 1947; 21:737-9.
 87. Karr RM. Bronchoprovocation studies in coffee worker's asthma. *J Allergy Clin Immunol* 1979; 64:650-4.
 88. Davison AG, Britton MG, Forrester JA, Davies RJ, Hughes DTD. Asthma in merchant seamen and laboratory workers caused by allergy to castor oil beans: analysis of allergens. *Clin Allergy* 1983; 13:553-61.
 89. Uragoda CG. Teamaker's asthma. *Br J Ind Med* 1970; 27:181-2.
 90. Gleich GJ, Welsh PW, Yunginger JW, Hyatt RE, Catlett JB. Allergy to tobacco: an occupational hazard. *N Engl J Med* 1980; 302:617-9.
 91. Newmark FM. Hops allergy and terpene sensitivity: an occupational disease. *Ann Allergy* 1978; 41:311-2.
 92. Flindt MLH. Pulmonary disease due to inhalation of derivatives of *Bacillus subtilis* containing proteolytic enzyme. *Lancet* 1969; 1:1177-81.
 93. Pepys J, Hargreave FE, Longbottom JL, Faux J. Allergic reactions of the lungs to enzymes of *Bacillus subtilis*. *Lancet* 1969; 1:1181-4.
 94. Mitchell CA, Gandeia B. Respiratory symptoms and skin sensitivity in workers exposed to proteolytic enzyme in detergent industry. *Am Rev Respir Dis* 1971; 104:11-12.
 95. Franz T, McMurray KD, Brooks S, Bernstein IL. Clinical immunologic and physiologic observations in factory workers exposed to *B subtilis* enzyme dust. *J Allergy* 1971; 42:170-80.
 96. Colten HR, Polakoff PL, Weinstein SF, Srieder DJ. Immediate hypersensitivity to hog trypsin resulting from industrial exposure. *N Engl J Med* 1975; 292:1050-3.
 97. Dolan TP, Meyers A. Bronchial asthma and allergic rhinitis associated with inhalation of pancreatic extracts. *Am Rev Respir Dis* 1974; 110:812-3.
 98. Tarlo SM, Shaikh W, Bell B, et al. Papain-induced allergic reactions. *Clin Allergy* 1978; 8:207-13.
 99. Baur X, Konig G, Bencze K, Fruhmman G. Clinical symptoms and results of skin test, RAST and bronchoprovocation test in thirty-three papain workers: evidence for strong immunogenic potency and clinically relevant "proteolytic effects of airborne papain. *Clin Allergy* 1982; 12:9-17.
 100. Cartier A, Malo JL, Pineau L, Dolovich J. Occupational asthma due to pepsin. *J Allergy Clin Immunol* 1984; 73:574-7.
 101. Pauwels R, Devos M, Callens L, van der Straeten M. Respiratory hazards from proteolytic enzymes. *Lancet* 1978; 1:669.
 102. Galleguillos F, Rodriguez JC. Asthma caused by bromelain inhalation. *Clin Allergy* 1978; 8:21-4.
 103. Flindt MLH. Allergy to alpha-amylase and papain. *Lancet* 1979; 1:1407-8.
 104. Bohner CB, Sheldon JM, Trenis JW. Sensitivity to gum acacia with a report of ten cases of asthma in printers. *J Allergy* 1940; 12:290-4.
 105. Fowler PBS. Printer's asthma. *Lancet* 1952; 2:755-7.
 106. Gelfand HH. The allergenic properties of vegetable gums. A case of asthma due to tragacanth. *J Allergy* 1943; 14:203-17.
 107. Cartier A, Malo JL, Forest F, Lafrance M, et al. Occupational asthma in snow crab processing workers. *J Allergy Clin Immunol* 1984; 74:261-9.
 108. Gaddie J, Legge JS, Friend JAR, Reid TMS. Pulmonary hypersensitivity in prawn workers. *Lancet* 1980; 2:1350-3.
 109. Jyo T, Kohmoto K, Katsutani T, et al. Hoya (sea-squirt) asthma. In: Frazier CA, ed. Occupational asthma. New York: Van Nostrand Reinhold Company, 1980; 209-29.
 110. Kobayashi S. Different aspects of occupational asthma in Japan. In: Frazier CA, ed. Occupational asthma. New York: Van Nostrand Reinhold Company, 1980; 229-44.
 111. Henschler D, Assman W, Meyer KO. The toxicology of the toluene diisocyanates. *Arch Toxicol* 1962; 19:364-87.
 112. Brooks SM. Bronchial asthma of occupational origin. *Scand J Work Environ Health* 1977; 3:53-72.
 113. Brugsch HG, Elkins HD. Toluene diisocyanate (TDI) toxicity. *N Engl J Med* 1963; 268:353-7.
 114. Pepys J, Pickering CAC, Breslin ABX, Terry DJ. Asthma due to inhaled chemical agents: toluene diisocyanate. *Clin Allergy* 1972; 2:225-36.
 115. Butcher BT. Inhalation challenge testing with toluene diisocyanate. *J Allergy Clin Immunol* 1979; 64:655-7.
 116. Taylor G. Immune response to tolylene diisocyanate (TDI) exposure in man. *Proc R Soc Med* 1970; 63:379-80.
 117. Avery SB, Stetson DM, Pan PM, Mathews KP. Immunological investigation of individuals with toluene diisocyanate asthma. *Clin Exp Immunol* 1969; 4:585-96.
 118. Butcher BT, Salvaggio JE, Weill H, Ziskind MM. Toluene diisocyanate (TDI) pulmonary disease: immunologic and inhalation challenge studies. *J Allergy Clin Immunol* 1970; 58:89-100.
 119. Karol MH, Joset HH, Alarie YC. Tolyt-specific IgE antibodies in workers with hypersensitivity to toluene diisocyanate. *Am Ind Hyg Assoc J* 1978; 39:454-8.
 120. Gallagher JS, Tse CST, Brooks SM, Bern-

- stein IL. Diverse profiles of immunoreactivity in toluene diisocyanate (TDI) asthma. *J Occup Med* 1981; 23:610-16.
121. Butcher BT, O'Neil CE, Reed MA, Salvaggio JE. Radioallergosorbent testing of toluene diisocyanate-reactive individuals using *p*-tolyl isocyanate antigen. *J Allergy Clin Immunol* 1980; 66:213-6.
122. Danks JM, Cromwell O, Buckingham JA, Newman-Taylor AJ, Davies RJ. Toluene-diisocyanate induced asthma: evaluation of antibodies in the serum of affected workers against a tolyl mono-isocyanate protein conjugate. *Clin Allergy* 1981; 11:161-8.
123. Baur X, Fruhmann G. Specific IgE antibodies in patients with isocyanate asthma. *Chest* 1981; 80(Suppl:73-6).
124. Butcher BT, Mapp C, Reed MA, O'Neill CE, Salvaggio JE. Evidence for carrier specificity of IgE antibodies detected in sera of isocyanate exposed workers (abstract). *J Allergy Clin Immunol* 1982; 69(Suppl:123).
125. Chen SE, Bernstein IL. The guinea pig model of diisocyanate sensitization I: immunological studies. *J Allergy Clin Immunol* 1982; 70:383-92.
126. Munn A. Hazards of isocyanates. *Ann Occup Hyg* 1965; 8:163-9.
127. Konzen RB, Craft BF, Scheel LD, Gorski CH. Human response to low concentrations of P,P'-diphenylmethane diisocyanate. *Am Ind Hyg Assoc* 1966; 27:121-7.
128. Tanser AR, Bourke MP, Blandford AG. Isocyanate asthma: respiratory symptoms caused by diphenyl-methane diisocyanate. *Thorax* 1973; 28:596-600.
129. Zeiss CR, Kanellakes TM, Bellone JD, Levitz D, Pruzansky JJ, Patterson R. Immunoglobulin E mediated asthma and hypersensitivity pneumonitis with precipitating anti-hapten antibodies due to diphenylmethane diisocyanate (MDI) exposure. *J Allergy Clin Immunol* 1980; 65:347-52.
130. Malo JL, Zeiss CR. Occupational hypersensitivity pneumonitis after exposure to diphenylmethane diisocyanate. *Am Rev Respir Dis* 1982; 125:113-6.
131. O'Brien IM, Harries MG, Burge PS, Pepys J. Toluene diisocyanate-induced asthma. Reactions to TDI, MDI, HDI and histamine. *Clin Allergy* 1979; 9:1-6.
132. Zammit-Tabona M, Sherkin M, Kijek K, Chan H, Chan-Yeung M. Asthma caused by dimethyl methane diisocyanate in foundry workers. Clinical, bronchoprovocation and immunologic studies. *Am Rev Respir Dis* 1983; 128:226-30.
133. Johnson A, Chan-Yeung M, MacLean L, et al. Respiratory abnormalities among workers in an iron and steel foundry in Vancouver. *Br J Ind Med* 1985; 42:94-100.
134. Malo JL, Ouimet G, Cartier A, Levitz D, Zeiss CR. Combined alveolitis and asthma due to hexamethylene diisocyanate (HDI) with demonstration of cross reactivity and immunologic reactivities to diphenyl methane diisocyanate (MDI). *J Allergy Clin Immunol* 1983; 72:413-9.
135. Baur X. Immunologic cross-reactivity between different albumin bound isocyanates. *J Allergy Clin Immunol* 1983; 71:197-205.
136. 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* 1977; 7:1-14.
137. Maccia CA, Bernstein IL, Emmett EA, Brooks SM. In vitro demonstration of specific IgE in phthalic anhydride hypersensitivity. *Am Rev Respir Dis* 1976; 113:701-4.
138. Zeiss CR, Patterson R, Pruzansky JJ, Miller M, Rosenberg M, Levitz D. Trimellitic anhydride-induced airway syndromes: clinical and immunologic studies. *J Allergy Clin Immunol* 1977; 60:96-103.
139. Patterson R, Addington W, Banner A, et al. Anti-hapten antibodies in workers exposed to trimellitic anhydride fumes: a potential immunopathogenic mechanism for the trimellitic anhydride pulmonary-disease-anemia syndrome. *Am Rev Respir Dis* 1979; 120:1259-67.
140. Patterson R, Zeiss CR, Roberts M, Pruzansky JJ, Wolkonsky P, Chacon R. Human anti-hapten antibodies in trimellitic anhydride inhalation reactions: immunoglobulin classes of anti-trimellitic anhydride antibodies and hapten inhibition studies. *J Clin Invest* 1978; 62:971-8.
141. Sale SR, Patterson R, Zeiss CR, Fiore M, Harris KE, Yawn D. Immune response of dogs and rabbits to intrabronchial trimellitic anhydride. *Int Arch Allergy Appl Immunol* 1982; 67:329-34.
142. Zeiss CR, Wolkonsky P, Chacon R, et al. Syndromes in workers exposed to trimellitic anhydride: a longitudinal clinical and immunologic study. *Ann Intern Med* 1983; 98:8-12.
143. Schlueter DP, Banaszak EF, Fink JN, Barboriak J. Occupational asthma due to tetrachlorophthalic anhydride. *J Occup Med* 1978; 20:183-7.
144. Milne J, Gandevia B. Occupational asthma and rhinitis due to western red cedar (*Thuja plicata*). *Med J Aust* 1967; 2:741-4.
145. Ishizaki T, Shida T, Miyamoto T, Matsumura Y, Mizuno K, Tomaru M. Occupational asthma from western red cedar dust (*Thuja plicata*) in furniture factory workers. *J Occup Med* 1973; 15:580-5.
146. Chan-Yeung M, Barton GM, MacLean L, Grzybowski S. Occupational asthma and rhinitis due to western red cedar (*Thuja plicata*). *Am Rev Respir Dis* 1973; 108:1094-102.
147. Chan-Yeung M. Immunologic and nonimmunologic mechanisms in asthma due to western red cedar (*Thuja plicata*). *J Allergy Clin Immunol* 1982; 70:32-7.
148. Chan-Yeung M, Veda S, Kus J, MacLean L, Enarson D, Tse K. Symptoms, pulmonary function and bronchial hyperreactivity in western red cedar compared to those in the office workers. *Am Rev Respir Dis* 1984; 130:1038-41.
149. Veda S, Enarson D, Kus J, McCormack G, MacLean L, Chan-Yeung M. Symptoms and pulmonary function in western red cedar workers related to duration of employment and dust exposure (abstract). *Am Rev Respir Dis* 1984; 129(Suppl:A152).
150. Evans E, Nicholls RJ. Histamine release by western red cedar (*Thuja plicata*) from lung tissue in vitro. *Br J Ind Med* 1974; 31:28-30.
151. Tse KS, Chan H, Chan-Yeung M. Specific IgE antibodies in workers with occupational asthma due to western red cedar. *Clin Allergy* 1982; 12:249-58.
152. Oostdam JV, Moreno R, Chan H, Paré PD, Schellenberg RR, Chan-Yeung M. Animal models of western red cedar asthma (abstract). *Am Rev Respir Dis* 1985; 131(Suppl:A9).
153. Belleau B, Burba J. Occupancy of adrenergic receptors and inhibition of catechol-o-methyl transferase by tropolones. *J Med Chem* 1963; 6:755-9.
154. Barton GM, MacDonald BF. The chemistry and utilization of western red cedar. Dept of Fisheries and Forestry, Canadian Forestry Service. Publication No. 1023. Ottawa: Information Canada, 1971.
155. Chan-Yeung M, Abboud R. Occupational asthma due to California redwood (*Sequoia sempervirens*) dust. *Am Rev Respir Dis* 1976; 114:1027-31.
156. Greenberg M. Respiratory symptoms following brief exposure to cedar of Lebanon (*Cedra libani*) dust. *Clin Allergy* 1972; 2:219-24.
157. Eaton KK. Respiratory allergy to exotic wood dust. *Clin Allergy* 1973; 3:307-10.
158. Pickering CAC, Batten JC, Pepys J. Asthma due to inhaled wood dust-western red cedar and iroko. *Clin Allergy* 1972; 2:213-8.
159. Sosman AJ, Schlueter DP, Fink JN, Barboriak JJ. Hypersensitivity to wood dust. *N Engl J Med* 1969; 281:977-80.
160. Booth BH, LeFoldt RH, Moffitt EM. Wood dust hypersensitivity. *J Allergy Clin Immunol* 1976; 57:352-7.
161. Hinojosa M, Moneo I, Dominguez J, Delgado E, Losada E, Alcover R. Asthma caused by African maple (*Triplachiton scheroxylon*) wood dust. *J Allergy Clin Immunol* 1984; 74:782-6.
162. Paggiaro PL, Cantalupi R, Filicri M, et al. Bronchial asthma due to inhaled wood dust: *Tan-ganyika aningre*. *Clin Allergy* 1980; 11:605-10.
163. Bush RK, Clayton D. Asthma due to Central American walnut (*Juglans olanchana*) dust. *Clin Allergy* 1983; 13:389-94.
164. Ordman D. Wood dust as an inhalant allergen. Bronchial asthma caused by kejaat wood (*Pterocarpus angolensis*). *S Afr Med* 1949; 23:973-5.
165. Bush RK, Yunginger JW, Reed CE. Asthma due to African zebrawood (*Microberlinia*) dust. *Am Rev Respir Dis* 1978; 117:601-3.
166. Hunter D, Milton R, Perry KMA. Asthma caused by the complex salts of platinum. *Br J Ind Med* 1945; 2:92-8.
167. Pepys J, Pickering CAC, Hughes EG. Asthma due to inhaled chemical agents: complex salts of platinum. *Clin Allergy* 1972; 2:391-6.
168. Cromwell O, Pepys J, Parish WE, Hughes EG. Specific IgE antibodies to platinum salts in sensitized workers. *Clin Allergy* 1979; 9:109-17.
169. Levene GM, Calnan CD. Platinum sensitivity treatment by specific hyposensitization. *Clin Allergy* 1971; 1:75-82.
170. McConnell LH, Fink JN, Schlueter DP, Schmidt MG. Asthma caused by nickel sensitivity. *Ann Intern Med* 1973; 78:888-90.
171. Block G, Chan-Yeung M. Asthma induced by nickel. *JAMA* 1982; 247:1600-2.
172. Malo JL, Cartier A, Doepner M, Nieboer E, Evans S, Dolovich J. Occupational asthma caused by nickel sulphate. *J Allergy Clin Immunol* 1982; 69:55-9.
173. Novey HS, Habib M, Wells ID. Asthma and IgE antibodies induced by chromium and nickel salts. *J Allergy Clin Immunol* 1983; 72:407-12.
174. Joules H. Asthma from sensitization to chromium. *Lancet* 1932; 2:182-3.
175. Smith AR. Chrome poisoning with manifestations of sensitization. *JAMA* 1931; 97:95-8.
176. Keskinen H, Kalliomaki PL, Alanko K. Occupational asthma due to stainless steel welding fumes. *Clin Allergy* 1980; 10:151-9.
177. Hartmann A, Wuthrich B, Bolognini G.

- Berufsbedingte lungenkrankheiten bei der hartmetallproduktion und bearbeitung ein allergische geschehen? Schweiz Med Wochenschr 1982; 112:1137-41.
178. Browne RC. Vanadium poisoning from gas turbine. Br J Ind Med 1955; 12:57-9.
179. Bruckner HC. Extrinsic asthma in a tungsten carbide worker. J Occup Med 1967; 9:518-9.
180. Pepys J, Pickering CAS. Asthma due to inhaled chemical fumes: amino ethyl ethanolamine in aluminum soldering flux. Clin Allergy 1972; 2:197-204.
181. Sterling GM. Asthma due to aluminum soldering flux. Thorax 1967; 22:333-7.
182. Ozhiganova VN, Ivanova IS, Dueva LA. Bronchial asthma in radio equipment assemblers. Sov Med 1977; 4:139-41.
183. Burge PS, Perks W, O'Brien IM, Hawkins R, Green M. Occupational asthma in an electronics factory. Thorax 1979; 34:13-8.
184. Burge PS, Perks WH, O'Brien IM, et al. Occupational asthma in an electronics factory. A case control study to evaluate aetiological factors. Thorax 1979; 34:300-7.
185. Burge PS, Harries MG, O'Brien IM, Pepys J. Bronchial provocation studies in workers exposed to the fumes of electronic soldering fluxes. Clin Allergy 1980; 10:137-49.
186. Burge PS, Edge G, Hawkins R, White V, Newman Taylor AJ. Occupational asthma in a factory making flux-cored solder containing colophony. Thorax 1981; 36:828-34.
187. Davies RJ, Hendrick DJ, Pepys J. Asthma due to inhaled chemical agents: ampicillin, benzylpenicillin, 6-aminopenicillanic acid and related substances. Clin Allergy 1974; 4:227-47.
188. Coutts II, Dally MB, Newman-Taylor AJ, Pickering CAC, Horsfield N. Asthma in workers manufacturing cephalosporins. Br Med J 1981; 283:950.
189. Kammermeyer JK, Mathews KP. Hypersensitivity to phenyl glycine and chloride. J Allergy Clin Immunol 1973; 52:73-84.
190. Pepys J, Pickering CAC, Loudon HWG. Asthma due to inhaled chemical agent: piperazine dihydrochloride. Clin Allergy 1972; 2:189-96.
191. Busse WW, Schoenwetter WF. Asthma from psyllium in laxative manufacture. Ann Intern Med 1975; 83:361-2.
192. Harries MG, Newman Taylor A, Wooden J, MacAuslan A. Bronchial asthma due to alpha-methyl dopa. Br Med J 1979; 1:1461.
193. Davies RJ, Pepys J. Asthma due to inhaled chemicals: the macrolide antibiotic spiramycin. Clin Allergy 1975; 5:99-107.
194. Fawcett IW, Pepys J, Erooga MA. Asthma due to glycol compound powder: an intermediate in production of salbutamol. Clin Allergy 1976; 6:405-9.
195. Greene SA, Freedman S. Asthma due to inhaled chemical agents: amprolium hydrochloride. Clin Allergy 1976; 6:105-8.
196. Fawcett IW, Pepys J. Allergy to a tetracycline preparation. Clin Allergy 1976; 6:301-3.
197. Feinberg SM, Watrous RM. Atopy to simple chemical compounds: sulphonchloramides. J Allergy 1945; 16:209-20.
198. Bourne MS, Flindt MLH, Walker JM. Asthma due to industrial use of chloramine. Br Med J 1979; 2:10-2.
199. Vallieres M, Cockcroft DW, Taylor DM, Dolovich J, Hargreave FE. Dimethyl ethanolamine-induced asthma. Am Rev Respir Dis 1977; 115:867-71.
200. Pepys J, Hutchcroft BJ, Breslin ABX. Asthma due to inhaled chemical agents: persulphate salts and henna in hairdressers. Clin Allergy 1976; 6:399-404.
201. Lam S, Chan-Yeung M. Ethylenediamine-induced asthma. Am Rev Respir Dis 1980; 121:131-5.
202. Slovak AJM. Occupational asthma caused by plastics blowing agent, azodicarbonamide. Thorax 1981; 36:906-9.
203. Graham V, Coc MJS, Davies RJ. Occupational asthma after exposure to a diazonium salt. Thorax 1981; 36:950-1.
204. Nagy L, Orosz M. Occupational asthma due to hexachlorophene. Thorax 1984; 39:630-1.
205. Hendrick DJ, Lane DJ. Formalin asthma in hospital staff. Br Med J 1975; 1:607-8.
206. Cockcroft DW, Hoepfner VH, Dolovich J. Occupational asthma caused by cedar urea formaldehyde particle board. Chest 1982; 82:49-53.
207. Frigas E, Filley WV, Reed C. Asthma induced by dust from urea formaldehyde foam insulating material. Chest 1981; 79:706-7.
208. Malo JL, Gagnon G, Cartier A. Occupational asthma due to heated freon. Thorax 1984; 39:628-9.
209. Silberman DE, Sorrell AH. Allergy in fur workers with special reference to paraphenylene diamine. J Allergy 1959; 30:11-8.
210. Cockcroft DW, Cartier A, Jones G, Tarlo SM, Dolovich J, Hargreave FE. Asthma caused by occupational exposure to a furan-based binder system. J Allergy Clin Immunol 1980; 66:458-63.
211. 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.
212. Ramsdale EH, Morris M, Hargreave FE. The diagnostic significance of increased bronchial responsiveness to methacholine in subjects with rhinitis (abstract). J Allergy Clin Immunol 1983; 71(Suppl:143A).
213. Burge PS. Single and serial measurements of lung function in the diagnosis of occupational asthma. Eur J Respir Dis 1982; 63(Suppl 123:47-59).
214. Cartier A, Pineau L, Malo JL. Monitoring of maximum expiratory peak flow rates and histamine inhalation tests in the investigation of occupational asthma. Clin Allergy 1984; 14:193-6.
215. Cockcroft DW, Kilan DN, Mellon JJA, Hargreave FE. Bronchial reactivity to inhaled histamine. A method and clinical survey. Clin Allergy 1977; 7:235-43.
216. Chai H, Farr RS, Fochlich LA, et al. Standardization of bronchial inhalation challenge procedures. J Allergy Clin Immunol 1975; 56:323-7.
217. Hargreave FE, Dolovich FE, Boulet LP. Inhalation provocation tests. In: Petty TL, Cherniack RM, eds. Seminars in Respiratory Medicine. Vol IV. 1983; 224-36.
218. Lam S, Tan F, Chan H, Chan-Yeung M. Relationship between types of asthmatic reaction, non-specific bronchial reactivity and specific IgE antibodies in patients with red cedar asthma. J Allergy Clin Immunol 1983; 72:134-9.
219. Pepys J, Hutchcroft BJ. Bronchial provocation test in etiology diagnosis and analysis of asthma. Am Rev Respir Dis 1975; 112:829-59.
220. Cockcroft DW, Cotton DJ, Mink JT. Non-specific bronchial hyperreactivity after exposure to western red cedar. Am Rev Respir Dis 1979; 119:505-10.
221. Siracusa A, Curradi F, Abritti G. Recurrent nocturnal asthma due to tolylene diisocyanate: a case report. Clin Allergy 1978; 8:195-201.
222. Wasserman S. Mediators of immediate hypersensitivity. J Allergy Clin Immunol 1983; 72:101-13.
223. Parish WE. Short term anaphylactic IgG antibodies in human sera. Lancet 1970; 2:591-4.
224. Dolovich J, Hargreave FE, Chalmers R, Shier KJ, Gaudie J, Bienenstock J. Late cutaneous allergic responses in isolated IgE dependent reactions. J Allergy Clin Immunol 1973; 52:38-46.
225. Solley G, Gleich G, Jordan R, Schroeter A. The late phase of the immediate wheal and flare skin reaction. Its dependence on IgE antibodies. J Clin Invest 1976; 58:408-20.
226. Tannenbaum S, Orcel H, Henderson W, Kaliner M. The biologic activity of mast cell granules. I. Elicitation of inflammatory response in rat skin. J Immunol 1980; 125:325-35.
227. DeShazo RD, Levinson AL, Dvorak HF, Davies RW. The late phase skin reaction: evidence for activation of the coagulation system in an IgE-dependent reaction in man. J Immunol 1979; 122:692-8.
228. Dvoracek JE, Yunginger JE, Kern EB, Hyatt RE, Gleich GJ. Induction of nasal late-phase reactions by insufflation of ragweed pollen extract. J Allergy Clin Immunol 1984; 73:363-8.
229. Lam S, Chan-Yeung M, LeRiche J, Kijck K, Phillips D. Cellular changes in bronchial lavage fluids following late asthmatic reaction in patients with red cedar asthma (abstract). Am Rev Respir Dis 1985; 131(Suppl:A42).
230. Lam S, Wong R, Chan-Yeung M. Nonspecific bronchial reactivity in occupational asthma. J Allergy Clin Immunol 1979; 63:28-34.
231. Kobayashi S. Different aspects of occupational asthma in Japan. In: Frazier CA, ed. 1980. Occupational asthma. New York: Van Nostrand Reinhold, 1980; 229-44.
232. Salvaggio J, ed. Occupational and environmental respiratory disease in NIAID task force report: asthma and other allergic disease. Washington, D.C.: U.S. Department of Health, Education and Welfare, May 1979 (NIH Publication No. 79-387).
233. Karr RM, David RJ, Butcher BT, et al. Occupational asthma. J Allergy Clin Immunol 1978; 61:54-64.
234. Newman Taylor AJ. Laboratory animal allergy. Eur J Respir Dis 1982; 123(Suppl:60-4).
235. NIOSH criteria for a recommended standard. Occupational exposure to diisocyanate. Washington, D.C.: U.S. Dept of Health, Education and Welfare, Sept. 1978 (NIOSH Publication No. 78-215).
236. Woolcock AJ, Colman MH, Jones MW. Atopy and bronchial reactivity in Australian and Melanesian populations. Clin Allergy 1978; 8:155-64.
237. Cockcroft DW, Berscheid BA, Murdock KY. Unimodal distribution of bronchial responsiveness to inhaled histamine in a random human population. Chest 1983; 83:751-4.
238. Balfour-Lynn L, Tooley M, Godfrey S. Relationship of exercise-induced asthma to clinical asthma in childhood. Arch Dis Child 1981; 56:450-4.
239. Enarson DA, Chan-Yeung M, Lam S, Vedal S, McCormack G. Does determination of bronchial reactivity add anything to prevalence studies of respiratory disease in their occupational setting (abstract). Am Rev Respir Dis 1984; 129:A160.

240. Newhouse ML, Tagg B, Popcock SL, McEwan AC. An epidemiologic study of workers producing enzyme washing powders. *Lancet* 1970; 1:689-93.
241. Burrows B, Halonen M, Barbee RA, Lebowitz MD. The relationship of serum immunoglobulin E to cigarette smoking. *Am Rev Respir Dis* 1981; 124:523-5.
242. Jones JG, Minty BD, Royston D, Royston JP. Carboxyhaemoglobin and pulmonary epithelial permeability in man. *Thorax* 1983; 38:129-33.
243. Hulbert WC, Walker DC, Jackson A, Hogg JC. Airway permeability to horseradish peroxidase in guinea pigs: the repair phase after injury by cigarette smoke. *Am Rev Respir Dis* 1981; 123:120-6.
244. Leskowitz S, Salvaggio JE, Schwarz HJ. An hypothesis for the development of atopic allergy in man. *Clin Allergy* 1972; 2:237-46.
245. Zetterstrom O, Osterman K, Machado L, Johansson SGO. Another smoking hazard: revised serum IgE concentration and increased risk of occupational allergy. *Br Med J* 1981; 283:1215-7.
246. Venables KM, Topping MD, Howe W, Luczynska CM, Hawkins R, Newman Taylor AJ. Interaction of smoking and atopy in the production of specific IgE antibodies against a hapten protein conjugate. *Br Med J* (in press).
247. Zamel N, Leroux M, Vanderdoelen JL. Airway response to inhaled methacholine in healthy nonsmoking twins. *J Appl Physiol* 1984; 56:936-9.
248. Adams WG. Long term effects on the health of men engaged in the manufacture of toluene diisocyanate. *Br J Ind Med* 1975; 32:72-8.
249. Moller DR, McKay RTK, Bernstein IL, Brooks S. Long term follow-up of workers with TDI asthma (abstract). *Am Rev Respir Dis* 1984; 129:A159.
250. Paggiaro PL, Loi AM, Rosso O, *et al*. Follow-up study of patients with respiratory disease due to toluene diisocyanate (TDI). *Clin Allergy* 1984; 14:463-9.
251. Burge PS. Occupational asthma in electronic workers caused by colophony fumes: follow-up of affected workers. *Thorax* 1982; 37:348-53.
252. Hudson P, Pineau L, Cartier A, Malo JL. Follow-up of occupational asthma due to various agents (abstract). *J Allergy Clin Immunol* 1984; 73:174A.
253. Simonsson B, Haeger-Aronsen B, Sjoberg A, Rolf C. Bronchial reactivity after ceased occupational exposure in aluminum-salt asthma in occupational lung disease. *Eur J Respir Dis* 1981; 62(Suppl:1-2).
254. Brostoff J, Mowbray JF, Kapoor A, Hoilwell SJ, Rudolf M, Saunders KB. 80% of patients with intrinsic asthma are homozygous for HLA-BW6. *Lancet* 1976; 2:872-3.
255. Venables VM, Topping MD, Nunn AJ, Howe W, Newman Taylor AJ. Follow-up of asthma caused by tetrachlorophthalic anhydride (abstract). *Am Rev Respir Dis* 1985; 131:A173.
256. Juniper CP, How MJ, Goodwin BFJ, Kinshott AIC. *Bacillus subtilis* enzymes: a 7 year clinical, epidemiological and immunological study of an industrial allergen. *J Soc Occup Med* 1977; 27:3-12.
257. Burney P, Chinn S. Defining asthma. A progress report. Paper presented at International Epidemiology Association Scientific Meeting, Vancouver, British Columbia, 1984. (Personal communication.)

Bakers' asthma

D. J. HENDRICK*, R. J. DAVIES† and J. PEPYS‡

* *Chest Department, Churchill Hospital, Oxford*, † *Department of Medicine, St Thomas' Hospital, London* and ‡ *Department of Clinical Immunology, Cardio-thoracic Institute, Brompton Hospital, London*

Summary

Bronchial provocation tests by 'occupational' exposure to flour provoked dual asthmatic reactions accompanied by rhinitis in two atopic bakers engaged in the manufacture of bread and pies. Ingestion tests with uncooked flour produced no reactions.

Skin prick tests with aqueous extracts of flour produced positive immediate reactions in both bakers, and negative reactions in nine of ten atopic asthmatic control subjects with no occupational exposure to flour. Intracutaneous tests, performed in one precipitin negative baker, gave dual responses. Precipitating antibodies to an aqueous extract of flour were found in the unconcentrated serum of the other baker, and not in ten control subjects.

Introduction

In recent years, bronchial provocation tests have been increasingly employed in the investigation of extrinsic asthma, both in the identification of relevant allergens and in the elucidation of underlying immunological mechanisms. Stresemann (1967) and Popa, George & Găvănescu (1970) demonstrated immediate asthmatic reactions in a number of flour workers following inhalation tests with nebulized extracts of flour and/or arthropod contaminants, and Lunn & Hughes (1967), using a nebulized grain weevil extract, noted a dual reaction in a laboratory worker. The immediate reaction was asthmatic, the late reaction chiefly 'alveolar'. More recently Warren, Cherniak & Tse (1974) observed dual respiratory reactions to nebulized extracts of grain dust in grain workers. The exact nature of the late responses was unclear.

This paper describes two bakers and reports for the first time dual asthmatic reactions to bronchial provocation tests with flour.

Materials and methods

Flour

Samples were obtained of the wheat and rye flours used by both bakers together with a sample of another wheat flour from a different source.

Correspondence: Dr D. J. Hendrick, Chest Department, Churchill Hospital, Oxford.

Skin tests

Modified prick tests were carried out with aqueous extracts of flour which had been freeze dried and reconstituted in concentrations of 1 mg/ml and 10 mg/ml in carbol-saline/glycerol (50/50, V/V).

Intracutaneous tests were carried out with 0.02 ml of the flour extracts prepared in the same concentrations in carbol-saline without glycerol.

Precipitin tests

Aqueous extracts of each flour sample, prepared in a concentration of 30 mg/ml, were used in agar gel double diffusion tests against the unconcentrated sera of both patients and control subjects.

Control subjects

Ten adult asthmatic subjects, who were not exposed to flour occupationally, but who were atopic (positive reactions had been obtained on routine skin prick testing to one or more of twenty-three common allergens), were selected at random from patients attending the out-patients department of the Brompton Hospital, London. Skin prick tests with the wheat and rye flour extracts were negative in all but one, and precipitin tests were negative in all ten. Intracutaneous tests were not performed.

Inhalation tests

The patients were admitted to hospital for bronchial provocation tests which were carried out in the mornings using the 'occupational' method previously described (Pickering, Batten & Pepys, 1972). The flour sample under investigation, like the lactose control, was heated overnight at 40°C to remove moisture and so create a finer dust. When cooled, the patients shook 250 g test samples of flour from one tray to another for up to 30 min in a confined environment. The exposures were supervised throughout and could have been terminated at once and appropriate treatment instituted had any untoward reaction occurred. Baseline readings of FEV₁ were taken during the hour preceding the exposure and at 10-min intervals during the following hour. Thereafter hourly readings were recorded until late evening. Blood total white cell counts and absolute eosinophil counts were measured before and 24 hr after the tests.

Ingestion tests

Capsules containing 1 g of flour were ingested. These tests were otherwise conducted in the same way as the inhalation tests.

Case reports

Case 1

Patient B.H., male, 33 years, first developed asthma and rhinitis at the age of 8 years. The symptoms were perennial, but worse in the summer and after exposure to house dust. In 1962 he began working in the family bakery, and in 1967 he first presented for allergy assessment. He was advised regarding environmental control of house and wheat dusts and given hyposensitization treatment with extracts of house dust and mixed cereal dusts with some relief. In 1969 he commenced using sodium cromoglycate and received a further hyposensitization course with a house dust mite preparation.

He subsequently became aware that moderately severe attacks of asthma and rhinitis occurred whenever rye flour was used at the bakery. Symptoms came on within 30 min of exposure and recurred during the evening after an intermediate period of relief.

On the two occasions he was admitted to hospital in September, 1972 and February, 1973 he was symptom free, and physical examination was normal.

Investigations. The haemoglobin was 17.4 g%, the total white cell count 6,400/cu mm and the absolute eosinophil count 720/cu mm. His chest X-ray was normal.

Pulmonary function tests.

	VC	FRC	TLC	RV/TLC	FEV ₁	FVC	FEV ₁ /FVC	D _L CO
Result	4,600	4,540	7,790	40.5%	3,245	5,280	61.5%	36.3
Predicted	4,480	3,350	6,130	26.8%	3,600	4,480	80.5%	29.5

Skin tests. Routine prick tests with 23 common allergens showed moderate reactions to grass pollen, house dust, *D. farinae* and *D. pteronyssinus*. There were weak reactions to tree pollen, cat fur, dog hair, feathers and horse hair.

Prick tests with extracts of his own rye and wheat flour and the wheat flour from another source all gave weak immediate reactions at a concentration of 1 mg/ml and moderate reactions at a concentration of 10 mg/ml.

Intracutaneous tests with extracts of each flour gave dual reactions. The diameters in mm of the immediate weals and late swellings are given in Table 1.

Precipitin tests. No precipitating antibodies were found in his unconcentrated serum to any of the flour extracts.

Provocation tests. Details of the provocation tests performed together with the maximum percentage falls in FEV₁ are shown in Table 2. The results are presented graphically in Figs 1 and 2.

Exposure to his own rye flour (test 2) provoked a marked immediate asthmatic reaction accompanied by rhinitis, and exposure was discontinued after 8 min. This was succeeded by a late asthmatic reaction of somewhat greater intensity. No crepitations were heard during either reaction.

Exposure for 5 min to rye flour following pre-treatment with beclomethasone dipropionate (test 3) produced an immediate asthmatic reaction of similar intensity as test 2, but the late component of the dual reaction was inhibited.

Table 1. Patient B.H., responses to intracutaneous tests

Concentration of flour extract	1 mg/ml		10 mg/ml	
	Immediate (mm)	Late (mm)	Immediate (mm)	Late (mm)
Test extract				
Control (Coca's Solution)	2 × 2	0	2 × 3	0
Own rye flour	10 × 17	0	12 × 18	25 × 45
Own wheat flour	11 × 18	30 × 34		
Other wheat flour	11 × 14	30 × 34		

Table 2. Patient B.H., details of provocation tests

Test	Date	Material	Amount (g)	Method	Duration (min)	Premedication	Max % fall from pre-exposure FEV ₁	
							During first hr after exposure	Between 1 and 24 hr after exposure
1	16-9-72	Lactose	250	Inhalation	30	—	4	19
2	17-9-72	Own rye flour	250	Inhalation	8	—	57	65
3	18-9-72	Own rye flour	250	Inhalation	5	Beclomethasone dipropionate, 200 µg, 30 min before test	62	20
4	17-2-73	Own wheat flour	250	Inhalation	30	—	41	45
5	18-2-73	Own wheat flour	250	Inhalation	30	Sodium cromoglycate, 40 mg, 15 min before test	13	19
6	19-2-73	Own wheat flour	1 × 1 capsule	Ingestion	—	—	1	14
7	20-2-73	Own wheat flour	10 × 1 capsule	Ingestion	—	—	5	9
8	21-2-73	Wheat flour of patient I.T.	250	Inhalation	30	—	34	23

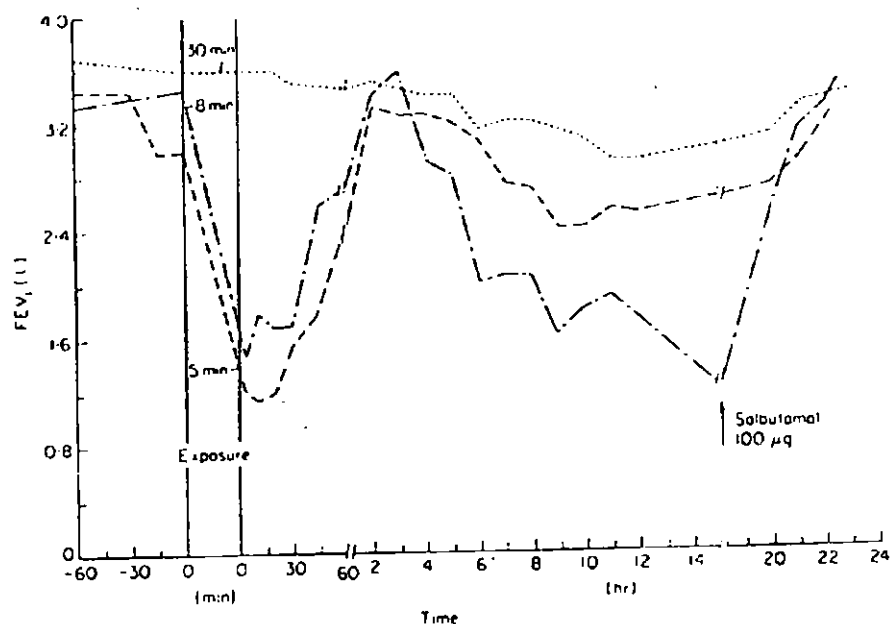


Fig. 1. Patient B.H. Results of provocation tests with rye flour. Effect of beclomethasone dipropionate., Lactose; ----, rye flour; -.-, rye flour, 30 min after beclomethasone dipropionate 200 µg.

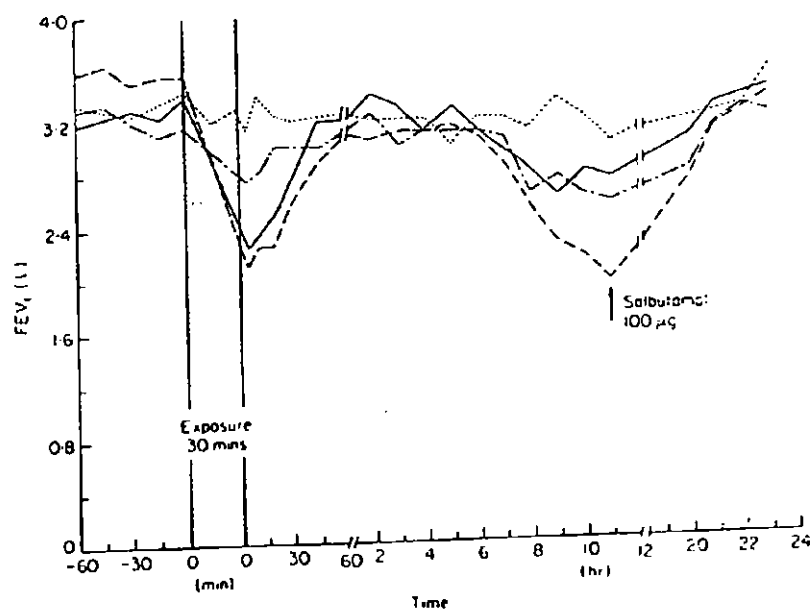


Fig. 2. Patient B.H. Results of provocation tests with wheat flour. ----, Own wheat flour; -.-, own wheat flour, 15 min after sodium cromoglycate 40 µg; —, wheat flour of patient I.T.;, own wheat flour by ingestion.

Exposure to his own wheat flour for 30 min (test 4) also produced a dual asthmatic reaction accompanied by rhinitis, but its severity was much less than that obtained with rye flour. Both components were inhibited by prior inhalation of sodium cromoglycate (test 5). A similar immediate reaction was obtained to the wheat flour used by patient I.T. (test 8), but this produced a less marked late reaction. No reactions were

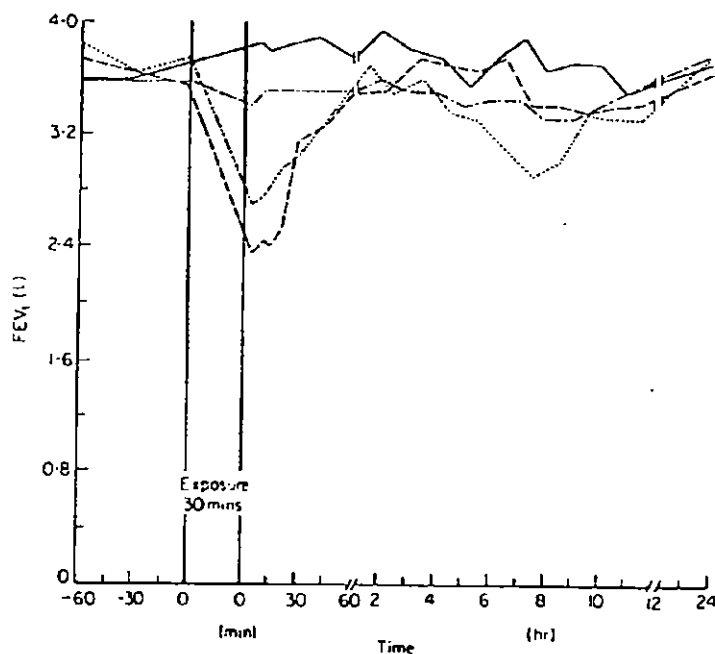


Fig. 3. Patient I.T. Results of provocation tests. Effect of beclomethasone dipropionate and sodium cromoglycate. —, Lactose; ·····, flour; ---, flour, 20 min after sodium cromoglycate 40 mg; — · —, flour, 30 min after beclomethasone dipropionate 200 µg.

obtained to the ingestion tests with uncooked flour (tests 6 & 7). Neither the total white cell count, nor the absolute eosinophil count varied significantly as a result of any of these provocation tests—though an absolute eosinophilia persisted throughout.

Case 2

Patient I.T., male, 33 years, came to the United Kingdom from Guyana in 1961. He was then symptom free, and began working in a meat pie factory. In 1968 he developed rhinitis which he noticed only at work when exposed to wheat flour. He changed his job with relief of symptoms but returned to the factory the following year. In 1971 rhinitis recurred—attacks following immediately after contact with flour. A year later asthma developed for the first time in his life. Attacks of wheezing, chest tightness and dry cough followed immediately after contact with flour and recurred during the early hours of the following night. The nocturnal cough distressed him most. He was free of symptoms at weekends and on holidays. He obtained some relief from sympathomimetic bronchodilators but had not used sodium cromoglycate.

At the time of his admission to hospital in August, 1972 he was symptom free and physical examination was normal.

Investigations. The haemoglobin was 14.6 g%, the total white cell count 6,000/cu mm, and the absolute eosinophil count 220/cu mm. His chest X-ray was normal.

Table 3. Patient J.T., details of provocation tests

Test	Date	Material	Amount (g)	Method	Duration (min)	Premedication	Max % fall from pre-exposure FEV ₁	
							During first hr after exposure	Between 1 and 24 hr after exposure
1	15-8-72	Latosec	250	Inhalation	30	—	0	5
2	16-8-72	Own wheat flour	250	Inhalation	30	—	28	23
3	18-8-72	Own wheat flour	250	Inhalation	30	Sodium cromoglycate, 40 mg, 20 min before test	6	8
4	22-8-72	Own wheat flour	250	Inhalation	30	Beclomethasone dipropionate, 200 µg, 30 min before test	34	7

Pulmonary function tests.

	VC	FRC	TLC	RV/TLC	FEV ₁	FVC	FEV ₁ /FVC	D _L CO
Result	4,000	1,910	5,350	25%	3,300	4,250	77%	20.4
Predicted	4,800	3,610	6,600	27%	3,860	4,800	81%	31.7

Skin tests. Routine prick tests with twenty-three common allergens showed positive immediate reactions to grass pollen, house dust and the house dust mite, *D. pteronyssinus*.

Prick tests with the extract of his own wheat flour at a concentration of 1 mg/ml produced no reactions, but at 10 mg/ml weakly positive weal and flare responses were produced. He was, however, taking oral antihistamines at the time, which are known to have an inhibitory effect. Intracutaneous tests were not performed.

Precipitin tests. Precipitating antibodies were demonstrated in unconcentrated serum to the extract of his own wheat flour but not to the other flour extracts.

Provocation tests. Details of the provocation tests performed, together with the maximum percentage falls in FEV₁, are shown in Table 3. The results are presented graphically in Fig. 3.

Exposure to his own wheat flour without premedication (test 2) led to a dual asthmatic reaction accompanied by rhinitis. No crepitations were heard but the single breath carbon monoxide gas transfer (D_LCO), measured approximately 6 hr after the exposure, was reduced by 24% of its pre-test level, to 15.5 ml/min/mmHg. The blood absolute eosinophil count 24 hr after the test was increased from 170 to 520 per mm³. No significant changes in D_LCO or blood eosinophil count occurred with the other three inhalation tests, and there was no significant change in the total white cell count or the body temperature with any test.

Pre-treatment with sodium cromoglycate inhibited both immediate and late asthmatic reactions (test 3), whereas the prior inhalation of beclomethasone dipropionate prevented only the late reaction (test 4).

Discussion

Dual asthmatic reactions following bronchial provocation tests have been reported to a number of substances including *Aspergillus fumigatus* (McCarthy & Pepys, 1971), house dust (Booij-Nord *et al.*, 1972), and the fumes from aluminium soldering flux (Pepys & Pickering, 1972). The dual asthmatic reactions described here in two bakers following inhalation of flour are the first to be reported, though tests with an extract of the grain weevil, *Sitophilus granarius* in a laboratory worker did produce a dual response (Lunn & Hughes, 1967). The immediate component was asthmatic, but the late component was more characteristic of allergic alveolitis. Dual respiratory responses were also observed in live grain workers following bronchial provocation tests with nebulized extracts of grain dust (Warren *et al.*, 1974). All experienced chest tightness during the late components when the maximum expiratory flow rates (at 50% of vital capacity) were reduced by at least 20% of the pre-exposure values. Wheezing was not a feature, however, nor were crepitations, and the authors remarked that the exact nature of these late reactions was unclear.

In our patients, the immediate and late reactions appear to have involved the airways. No crepitations were heard at any time, though the D_LCO did fall by 24% during the late component of the reaction given by patient I.T. A similar fall in D_LCO

was observed during a late asthmatic reaction to inhaled benzyl penicillin in a penicillin worker (Davies, Hendrick & Pepys, 1974) but the D_LCO did not alter during late asthmatic reactions of similar magnitude to wood dusts (Pickering *et al.*, 1972), soldering flux fumes (Pepys & Pickering, 1972), or piperazine (Pepys, Pickering & Loudon, 1972). The significance of this finding is, at present, unclear.

Although we have shown previously that sensitized workers engaged in the production of ampicillin from benzyl penicillin may give similar late asthmatic reactions to the relevant antibiotic whether inhaled or ingested, the ingestion tests in these bakers with up to 10 g of uncooked flour produced no reactions. This is possibly attributable to loss of antigenicity by digestion, though, in Japan, where buckwheat is widely used in food and its chaff in padding pillows, asthmatic reactions to both inhaled and ingested buckwheat have been described (Matsumura *et al.*, 1964; Nakamura, 1972).

In both patients, pre-treatment with sodium cromoglycate inhibited both immediate and late components of the dual reactions. By contrast, pre-treatment with the corticosteroid aerosol, beclomethasone dipropionate, had no effect on the immediate responses though the late responses were inhibited. These effects are characteristic and have been reported previously (Pepys *et al.*, 1974).

Both patients were atopic subjects in that both gave immediate skin prick test reactions to a number of common allergens on routine testing. Positive prick tests were also obtained to extracts of the flour samples studied. These, together with the immediate asthmatic and nasal reactions following the inhalation provocation tests, are suggestive of IgE mediated type 1 hypersensitivity (Gell & Coombs, 1968). The mechanism underlying late asthmatic reactions is controversial. Type 3 hypersensitivity, mediated by complement activating immune complexes of antigen and precipitating antibody has been favoured for some years but correlations between precipitin levels and disease have proved poor, and Hargreave *et al.* (1974) have recently suggested that non-precipitating IgE antibodies alone may mediate both immediate and late components of dual asthmatic reactions. One of the two bakers described here did show a positive precipitin test to flour, but the other, who was clinically the more sensitive, did not.

As a result of these investigations the relevance of inhaled flour to the development of asthma and rhinitis was confirmed in both bakers, and the potential protective value of sodium cromoglycate was established. By subsequently avoiding undue exposure and by taking sodium cromoglycate regularly, both bakers were able to continue with their occupations.

Acknowledgments

We are grateful to Miss J. Mitchell for preparing the flour extracts and for carrying out the precipitin tests, to Miss R. Hawkins, S.R.N., for performing skin prick tests on the control subjects and to the Clinical Research Board of the Brompton Hospital for financial support (D.J.H.). The illustrations were kindly prepared by the Medical Illustration Department of the Radcliffe Infirmary, Oxford.

References

- BOON-NOORD, H., DE VRIES, K., SLUETER, H.J. & ORIE, N.G.M. (1972) Late bronchial obstructive reaction to experimental inhalation of house dust extract. *Clinical Allergy*, 2, 43.
- DAVIES, R.J., HENDRICK, D.J. & PEPYS, J. (1974) Asthma due to inhaled chemical agents: ampicillin, benzyl penicillin, 6 amino penicillanic acid and related substances. *Clinical Allergy*, 4, 227.

- GELL, P.G.H. & COOMBS, R.R.A. (1968) *Clinical Aspects of Immunology*. Blackwell Scientific Publications, Oxford.
- HARGREAVE, F.E., DOLOVICH, J., ROBERTSON, D.G. & KERRIGAN, A.T. (1974) The late asthmatic responses. *Canadian Medical Association Journal*, **110**, 415.
- LUNN, J.A. & HUGHES, D.T.D. (1967) Pulmonary hypersensitivity to the grain weevil. *British Journal of Industrial Medicine*, **24**, 158.
- MATSUMURA, T., TATENO, K., YUGAMI, S. & KUROUME, T. (1964) Six cases of buckwheat asthma induced by buckwheat flour attached to buckwheat chaff in pillows. *Journal of Asthma Research*, **1**, 219.
- MCCARTHY, D.S. & PEPYS, J. (1971) Allergic bronchopulmonary aspergillosis. Clinical immunology: (2) skin, nasal and bronchial tests. *Clinical Allergy*, **1**, 415.
- NAKAMURA, S. (1972) On occupational allergic asthma of different kinds newly found in our allergy clinic. *Journal of Asthma Research*, **10**, 37.
- PEPYS, J., DAVIES, R.J., BRESLIN, A.B.X., HENDRICK, D.J. & HUTCHCROFT, B.J. (1974) The effects of inhaled beclomethasone dipropionate (Becotide) and sodium cromoglycate on asthmatic reactions to provocation tests. *Clinical Allergy*, **4**, 13.
- PEPYS, J. & PICKERING, C.A.C. (1972) Asthma due to inhaled chemical fumes—amino-ethyl ethanolamine in aluminium soldering flux. *Clinical Allergy*, **2**, 197.
- PEPYS, J., PICKERING, C.A.C. & LOUDON, H.W.G. (1972) Asthma due to inhaled chemical agents—piperazine dihydrochloride. *Clinical Allergy*, **2**, 189.
- PICKERING, C.A.C., BATTEN, J.C. & PEPYS, J. (1972) Asthma due to inhaled wood dusts—Western Red Cedar and Iroko. *Clinical Allergy*, **2**, 213.
- POPA, V., GEORGE, S.A. & GĂVĂNESCU, O. (1970) Occupational and non-occupational respiratory allergy in bakers. *Acta allergologica*, **25**, 159.
- STRESEMANN, E. (1967) Results of bronchial testing in bakers. *Acta allergologica*, **22** (Suppl. 8), 99.
- WARREN, P., CHERNIAK, R.M. & TSE, K.S. (1974) Hypersensitivity reactions to grain dust. *Journal of Allergy and Clinical Immunology*, **53**, 139.

Evaluation du degré de sensibilisation aux allergènes professionnels et de l'incidence de l'asthme dans une population de boulangers d'une industrie de la région liégeoise (*)

M.P. HERENG¹, S. DEMARTEAU², J. LAMOTTE¹, P. BARTSCH¹

¹ Institut E. Malvoz de la Province de Liège - Physiopathologie du Travail
Quai du Barhou, Liège

² Service Médical Interentreprises - Dir. L. Schillings
Bd. de la Sauvenière, Liège

RESUME

Nous avons réalisé dans cette étude une évaluation allergologique de 26 boulangers d'une boulangerie industrielle (anamnèse, tests cutanés, dosages sanguins, épreuves respiratoires avec tests de provocation bronchique à la farine) versus 24 sujets témoins.

Quinze boulangers étaient exempts de toute symptomatologie. Huit sujets souffrant de rhino-conjonctivite en relation avec leur travail n'ont présenté aucun test positif, on observe cependant comme chez les boulangers asymptomatiques, et plus fréquemment que chez les témoins, des réactions douteuses pour le Dermatophagoides Farinae.

Chez les 3 boulangers souffrant d'asthme au contact de la farine, les tests cutanés furent positifs au blé et/ou au seigle alors que le RAST ne l'était que chez l'un d'entre eux. Ils présentèrent tous trois un syndrome obstructif sévère immédiatement après le test de provocation bronchique spécifique.

D'une façon générale, les tests cutanés se sont révélés plus sensibles que le RAST, et le test de provocation bronchique à la farine s'est avéré hautement spécifique pour la recherche d'asthme par sensibilisation à la farine.

SAMENVATTING

In deze studie, hebben we een allergologische evaluatie verricht bij 26 bakkers van een industriële bakkerij (anamnese, huidtesten, bloeddoseringen, ademhalingsproeven bevattend bronchiale provokatietest met bloem) versus 24 controlepersonen.

Vijftien bakkers waren vrij van alle symptomatologie. Acht personen lijdend aan rhinoconjunctivitis in verband met hun werk hebben geen positieve test vertoond; men merkt niettemin op, zoals bij de asymptomatische bakkers en vaker dan bij de controles, twijfelachtige reacties voor de Dermatophagoides Farinae.

Bij de 3 bakkers lijdend aan astma door contact met bloem, werden de huidtesten voor tarwe en/of voor rogge positief, terwijl de RAST slechts bij een van hen positief was. Ze vertoonden alle drie een

ernstig obstructief syndroom onmiddellijk na de specifieke bronchiale provokatietest.

Over het algemeen, zijn de huidtesten gevoeliger gebleken dan de RAST en de bronchiale provokatietest met bloem is ten eerste specifiek gebleken voor het onderzoek van astma door sensibilisatie voor bloem.

1. Introduction — Epidémiologie

Le premier cas d'asthme chez un boulanger fut décrit par Bernardo Ramazzini en 1700.

L'asthme allergique du boulanger, communément appelé farinose, représente une proportion importante des allergies respiratoires professionnelles. Cette sensibilisation semble toutefois diminuer avec les moyens modernes de production (Sutton et coll., 1984, Popa et coll., 1970). La prévalence d'allergie respiratoire chez les boulangers varie selon les études de 3,1 à 28 % (Thiel, H., 1983).

En Belgique, depuis 25 ans, 1.073 cas furent reconnus au F.M.P. dont 700 depuis 1981, soit 1,2 % des maladies professionnelles respiratoires (y compris la silicose). Chaque année, en moyenne 87 nouvelles demandes d'indemnisation sont introduites, le pourcentage de reconnaissance s'élève à 75 %. Parmi ces 1.073 cas reconnus on dénombre 816 boulangers; 934 sujets proviennent de la boulangerie industrielle, les autres cas émanant du secteur agricole, d'institutions hospitalières, de grandes surfaces....

Le F.M.P. continue actuellement à indemniser 879 maladies professionnelles chez des boulangers dont 816 pour raison d'asthme et 8 pour autres affections respiratoires. Par comparaison, en R.F.A., 369 nouveaux cas sont introduits par an dont 20 % seulement sont indemnisés. En effet, la législation allemande ne prévoit l'indemnisation que lorsque l'invalidité atteint 20 % au moins et oblige l'ouvrier à quitter son emploi. Ce second critère est fortement dissuasif

(*) Communication donnée le 9 octobre 1987 à la Société belge de Médecine et d'Hygiène du travail d'expression française.

compte tenu des désavantages sociaux et financiers qu'une reconversion occasionne chez ces travailleurs issus, pour 80 % des cas, de petites entreprises familiales (Thiel H., 1983).

Le taux d'affection respiratoire atteint, selon Thiel, 8,4 % parmi les apprentis, 12,4 % chez les boulangers ayant moins de 15 ans d'ancienneté et 23,4 % chez ceux qui ont plus de 15 ans d'ancienneté.

Le délai d'apparition de la rhino-conjonctivite varie fortement, la moyenne étant de 9 ans. Pour l'asthme, cette moyenne se situe entre 10 et 14 ans (Popa et coll., 1970).

2. Ethio-pathologie

A l'origine des symptômes respiratoires se retrouve un mécanisme d'hypersensibilité immédiate de type I à médiation IgE. Les réactions asthmatiques tardives ne sont cependant pas rares, se déroulant 4 à 6 heures après le premier contact allergénique. Le stimulus initial est formé par la liaison entre l'allergène et les anticorps IgE. Ceci provoque une activation des mastocytes. Les médiateurs broncho-actifs libérés par les cellules (leucotriènes, histamine, prostaglandines) provoquent une bronchoconstriction immédiate. Les médiateurs chimiotactiques qui se libèrent du mastocyte (ECF, NCF — HMW, PAF, ...) entraînent un apport de leucocytes, neutrophiles et éosinophiles. Ces leucocytes sont activés et sécrètent à leur tour des médiateurs broncho-actifs qui provoquent la bronchoconstriction tardive (Pauwels R., in *Allergologie Clinique*, 1985).

D'un point de vue clinique, on observe de la toux, des expectorations accompagnant une dyspnée asthmatiforme à prédominance hivernale lorsque l'aération du local de travail est plus mauvaise, les symptômes apparaissent immédiatement après le contact mais surtout en fin de travail, c'est-à-dire le matin chez ces travailleurs nocturnes. S'y associent fréquemment rhinite et/ou conjonctivite (Charpin J., 1986).

Les allergènes en cause connus de longue date appartiennent essentiellement aux protéines des grains de céréales et des farines qui en sont extraites. D'autres pneumallergènes, d'ordre différent, sont à l'origine de certaines sensibilisations. Diverses études ont mis en évidence le rôle des contaminants de la farine tels les arthropodes (Thiel H., 1983, Magis N., 1954, Neuwell E. et Goo D., 1936, Loschiavo S., 1970, Sutton et coll., 1984), les bactéries et moisissures (Klaustermeyer et coll., 1977).

Antigènes les plus fréquemment rapportés dans la littérature :

a) Les arthropodes

Le rôle des teignes de la farine du genre *Ephesia* appartenant à l'ordre des lépidoptères est bien connu. A l'ordre des coléoptères appartient le charançon du blé, il est responsable de sensibilisations de type réaginique ou plus rarement d'alvéolites

allergiques extrinsèques de type III chez les travailleurs de la farine (Moricheau-Beauchant et coll., 1964). Il est encore appelé communément « punaise de son », « charançon rouge », « coléoptère de la farine », « coléoptère confus de la farine », il s'agit des *Tribolium Confusum* et *Castaneum*. La plupart des espèces *Tribolium* sont sauvages et localisés principalement dans les régions intertropicales.

Trois d'entre elles sont devenues synanthropes et à peu près cosmopolites : *Tribolium Confusum*, *Castaneum* et *Destructor*. Ces insectes sont très résistants et capables de survivre sur une grande variété de matières alimentaires dont le transport commercial intercontinental leur a permis d'atteindre des régions qu'elles n'auraient jamais colonisées autrement. Omnivores, on les retrouve dans plus de 100 types d'entrepôts. Les farines sont cependant le plus fréquemment infestées, elles prennent alors une coloration grisâtre et parfois une odeur désagréable. Vivant le plus souvent en lieu clos et chauffé, on n'observe pas de variation saisonnière de leur activité. Celle-ci diminue cependant avec la température, les adultes survivent durant l'hiver dans un état « d'hibernation » relatif. Leur longévité varie de 3 mois à 3 ans (Magis N., 1954, Neuwell et Goo, 1936).

Les mesures d'éviction et d'élimination comprennent la fumigation à l'aide d'insecticides, le surchauffage (une température inférieure à 70° n'altère pas la farine ni les céréales), l'utilisation de sachets étanches : sacs de Polyéthylène fermés à chaud (Loschiavo S., 1970).

A côté de ces espèces décrites plus longuement, les dermatophagoides farineae et tyrophagus putrescentiae, acariens domestiques, sont connus pour donner des sensibilisations plus fréquentes et/ou plus importantes chez les boulangers (Baldo et coll., 1980, Popa et coll., 1970, Sutton et coll., 1984).

b) Les protéines de céréales

La diversité des allergènes provient du nombre de protéines présentes dans chaque type de grains et de la variété des céréales susceptibles de provoquer une sensibilisation (Sutton et coll., 1984). Parmi ces céréales figurent essentiellement le froment et le seigle mais aussi l'orge qui leur est apparenté, le riz, l'avoine et le maïs, bien que ces derniers soient phylogénétiquement différents et non utilisés par le secteur qui nous occupe.

Blands et coll. (1976) démontrent 40 antigènes différents dans un extrait de farine de blé.

Sutton et coll. (1984) isolent et purifient par méthode électrophorétique 3 protéines de la farine de blé présentant une haute spécificité vis-à-vis des IgE issues de sérum de patients sensibilisés à cette céréale. Ils observent toutefois une grande diversité d'anticorps d'un sérum à l'autre. Ils déterminent également la nature de ces protéines, la plus grande partie appartenant au groupe des albumines et globulines plutôt qu'au groupe gliadine et gluténine moins solubles.

3. Objectifs

Cette étude poursuit deux buts :

1. Evaluer le degré de sensibilisation aux allergènes auxquels les boulangers sont professionnellement exposés en comparaison avec une population témoin professionnellement non exposée.
2. Objectiver l'incidence d'asthme extrinsèque parmi les boulangers-pâtisseries d'une boulangerie industrielle.

4. Matériel et méthodes

L'entreprise concernée est une boulangerie-pâtisserie industrielle de la région liégeoise occupant 36 boulangers, 19 briochoirs, 14 pâtisseries, 20 expéditeurs, 3 mécaniciens, 55 camionneurs et 22 employés. Le bâtiment de production renferme deux halls de boulangerie et la pâtisserie, disposés parallèlement. Des dosages atmosphériques de farine furent réalisés durant 8 heures, le long de ces lignes de fabrication allant du pétrin à l'emballage.

Les endroits particulièrement enfarinés sont :

- Le pétrissage où la farine stockée en cuve est déversée par commande manuelle au-dessus du pétrin.
- Les lignes où se déroulent différents stades de la fabrication du pain : pesage, façonnage.
- Le feuilletage où, dans un local isolé, un conditionnement d'air maintient une température constante, mais également une grande quantité de farine en suspension.
- L'enfournement.
- Le ramassage.

La population témoin comporte 24 sujets dépourvus d'antécédents héréditaire et personnel d'allergie, non exposés professionnellement à la farine.

Les 26 boulangers et pâtisseries ou briochoirs constituant le groupe étudié appartiennent aux différents points de production de l'entreprise, qu'ils soient symptomatiques d'allergie ou non. Ils seront par la suite confondus dans le terme « boulangers ».

Furent pris en compte l'âge des sujets (entre 20 et 60 ans), le tabagisme, les antécédents allergiques et autres, la durée d'exposition professionnelle, le type de symptômes manifestés. Chaque sujet a subi une anamnèse médicale et professionnelle, des tests cutanés (prick-tests Benard) à l'aide de pneumallergènes courants : poussière de maison, dermatophagoides pteronyssinus, dermatophagoides farinae, épithélia de chiens, de chats, pollens de graminées, et d'allergènes professionnels : grains de froment, de seigle, d'orge, d'avoine, de riz et de maïs, farines mélangées, farine de blé entier, farine de seigle, *Tribolium confusum*.

Nous avons systématiquement mesuré l'éosinophilie sanguine relative et absolue, les IgE totales et spécifiques (Prist et Rast de Pharmacia) reprenant quelques pneumallergènes courants (dermatophagoides pteronyssinus et dermatophagoides farinae, pol-

lens de graminées, mixture d'épithélia) et des allergènes professionnels (froment, seigle, orge, avoine, riz, levure, gluten).

Une spirométrie fut enfin réalisée chez chaque personne lors du test de provocation bronchique spécifique à la farine avec enregistrement des CV, VEMS, MEF 50, capacité synchrone avant l'épreuve et 1 min puis 15 min après. Le test de provocation bronchique spécifique consistait à faire inhaler, via un embout buccal, de l'air chargé des farines utilisées dans l'entreprise pendant 3 fois 1 min. Un contrôle du tracé d'asynchronisme ventilatoire enregistré par la méthode de l'interruption du courant aérien (Petit J.M. et coll., 1971) fut réalisé avant le test, entre chaque période d'inhalation et 15 min après, en complément des mesures précédentes. 24 sujets témoins furent complètement investigués de même que 26 boulangers (Tableau 1). Les moyennes d'âge de ces deux populations sont respectivement de 36,3 ans et 34,7 ans.

Tableau 1
Symptômes rapportés

	Témoins	Boulangers-Pâtisseries
Nombre	24	26
Age	23 → 58 (m = 36,3)	22 → 51 (m = 34,7)
Tabac	12 NF 9 F 3 AF	16 NF 10 F
Durée d'exposition	—	18 mois → 39 ans (m = 15,5 ans)
Antécédents allergiques	—	6
Symptômes	—	7 rhinite 1 prurit oculaire 3 asthme + R.C.

Parmi les témoins on dénombre 12 non-fumeurs, 9 fumeurs et 3 anciens fumeurs, parmi les boulangers 16 non-fumeurs et 10 fumeurs. Dans ce dernier groupe, la durée d'exposition varie de 18 mois à 39 ans, avec une moyenne de 15,5 ans.

Les témoins sont bien entendu asymptomatiques alors qu'on relève parmi les boulangers, lorsqu'ils sont au contact de la farine : 7 cas de rhinite, 1 prurit oculaire, 3 cas d'asthme avec rhino-conjonctivite.

Les tests statistiques appliqués furent ceux du X^2 , du X^2 corrigé, du t de Student et le test d'indépendance.

5. Résultats

1. *Tests cutanés* : ils furent exprimés en scores allant de 0 à ++++. Le test est considéré comme positif s'il est supérieur à ++ (Thiel H., 1983, Stevens E. in Allergologie Clinique, 1985, Boutin et coll. in Allergologie, 1986).

Les allergènes sont séparés en 2 groupes :

1) allergènes courants

poussière de maison (Hd), dermatophagoïdes pteronyssinus (Dt Pt), dermatophagoïdes farinae (Dt Fa), pollens de graminées (G), épithélium de chiens (Dg), épithélium de chats (Ct);

2) allergènes professionnels

grains de froment (F), grains de seigle (S), grains d'orge (O), grains d'avoine (A), grains de riz (R), grains de maïs (M), farines mélangées (Fm), farine de blé entier (Fh), farine de seigle (Fs), Tribolium Confusum (Tc).

Le tableau II nous montre le nombre de sujets ayant au moins une réponse positive pour chaque groupe d'allergènes. Concernant les allergènes courants, on observe 25 % de réactions positives chez les témoins et 30,7 % chez les boulangers, sans différence statistiquement significative entre les deux populations. Concernant les allergènes professionnels, on observe un sujet témoin réagissant à l'ensemble des pneumallergènes, en le réinterrogeant, nous apprendrons qu'il présente une urticaire au contact des foin. Parmi les boulangers, 3 d'entre-eux réagissent à l'un ou l'autre allergène professionnel, il s'agit des 3 asthmatiques.

Tableau II

Tests cutanés : sujets ayant au moins une réponse positive par groupe d'allergènes

Allergènes	Témoins n = 24		Boulangers n = 26	
	n	%	n	%
courants n = 6	6	25 %	8	30,7 %
professionnels n = 10	1	4,2 %	3	11,5 %

Lorsque l'on compare la sensibilisation cutanée pour des acariens domestiques et des contaminants de la farine (Tableau III), on n'observe pas de différence statistiquement significative entre les deux populations.

Tableau III

Tests cutanés : sujets positifs au Dt Pt, Dt Fa, T.c.

Allergènes	Témoins n = 24		Boulangers n = 26	
	n	%	n	%
Dt Pt	6	25 %	5	19,2 %
Dt Fa	5	20,8 %	5	19,2 %
T.c.	2	8,3 %	2	7,7 %

Lorsque l'on scinde la population de boulangers en 3 groupes en fonction des symptômes, on observe au tableau IV que la majorité des boulangers réagissant aux allergènes courants sont asymptomatiques, que 2 boulangers asthmatiques sont sensibilisés pour ces allergènes courants, qu'aucun sujet présentant de la rhino-conjonctivite ne réagit ni aux allergènes courants ni aux allergènes professionnels.

Tableau IV

Tests cutanés : résultats positifs pour au moins un allergène du groupe en fonction des symptômes chez les boulangers

Allergènes	Asympto. n = 15		Rhino-conj. n = 8		Asthme n = 3	
	n	%	n	%	n	%
courants n = 6	6	40 %	0	0 %	2	66,6 %
professionnels n = 10	0	0 %	0	0 %	3	100 %

Au tableau V, on note à nouveau la grande majorité des réactions positives pour les acariens et les contaminants de la farine chez les boulangers asymptomatiques.

Tableau V

Tests cutanés : résultats positifs aux Dt Pt, Dt Fa, T.c. en fonction des symptômes chez les boulangers

Allergènes	Asympto. n = 15		Rhino-conj. n = 8		Asthme n = 3	
	n	%	n	%	n	%
Dt Pt	4	26,6 %	0	0 %	1	33,3 %
Dt Fa	5	33,3 %	0	0 %	0	0 %
T.c.	2	13,3 %	0	0 %	0	0 %

En ce qui concerne ces 3 derniers allergènes, on observe généralement chez un même individu, des réactions positives aux 3 arthropodes, les personnes sensibilisées au Tribolium Confusum le sont toujours, et de façon plus importante, aux dermatophagoïdes pteronyssinus, qu'il s'agisse de témoins ou de boulangers exposés.

2. Dosages sanguins : au tableau VI, les valeurs d'éosinophilie relative et absolue sont en moyenne basses dans les deux populations, sans relation avec la présence de symptôme chez les boulangers. Les valeurs moyennes d'IgE totales sont également généralement basses, les plus élevées étant observées

chez les sujets témoins et asymptomatiques, seul un sujet asthmatique atteint la valeur de 347 KU/L. Ces résultats reflètent la faible valeur diagnostique des dosages d'éosinophiles et d'IgE totales circulants.

Le dosage d'IgE spécifiques (RAST) est exprimé en scores de 0 à 4. Au tableau VII, nous avons repris les résultats positifs (score supérieur à 2) selon le même principe que pour les tests cutanés.

On n'observe aucune réaction positive chez les sujets témoins pour aucun allergène testé; parmi les boulangers, le taux de réaction est faible, une seule réaction positive par groupe d'allergènes. Le tableau

VIII détaille ces réactions chez les boulangers en fonction des symptômes. Il nous permet de souligner le fait qu'un seul boulanger asthmatique présente des réactions aux allergènes professionnels atteignant un score de 3. Ceci montre le manque de sensibilité du RAST lorsque l'on ne tient compte que des scores 3 et 4.

Il est intéressant de souligner que 6 boulangers présentent un RAST de score 1 ou 2 pour les dermatophagoides farineux, un seul possède également des IgE circulantes pour les dermatophagoides pteronyssinus.

Tableau VI

Dosages sanguins : éosinophilie relative et absolue. Moyenne pour chaque groupe de sujets

	Témoins n = 24	Boulangers n = 26				T/B t de Student
		Asympto. n = 15	Rhino-Conj. n = 8	Asthme n = 3	Total n = 26	
Eosinophilie relative N : 0-6 %	3 (1 → 8)	2,61 (1,5 → 6)	2,57 (1,5 → 4)	2,89 (1 → 5)	2,69	t = 1,482 P = 0,152
Eosinophilie absolue N : 0-0,4.10 ³ /mm ³	0,22 (0,05 → 0,71)	0,173 (0,09 → 0,39)	0,158 (0,1 → 0,21)	0,157 (0,12 → 0,25)	0,17	t = 0,664 P = 0,514
IgE Totales N : < 200 KU/L	112,2 (0,5 → 1300)	85,5 (0,63 → 323)	18,6 (0,5 → 56)	158 (35 → 347)	87,4	t = 0,935 P = 0,36

Tableau VII

RAST : sujets ayant au moins une réaction positive pour un allergène

Allergènes	Témoins n = 24		Boulangers n = 26	
	n	%	n	%
courants n = 4	0	0 %	1	3,8 %
professionnels n = 7	0	0 %	1	3,8 %
Dt Pt	0	0 %	1	3,8 %
Dt Fa	0	0 %	1	3,8 %

Par comparaison, dans la population témoin 3 sujets ont de tels scores pour à la fois Dt Pt et Dt Fa. Ces résultats n'atteignent toutefois pas le seuil de signification statistique.

3. *Test de provocation à la farine* : les valeurs de base des différents paramètres fonctionnels respiratoires sont normaux avant le test de provocation bronchique spécifique (TPBS), tant chez les témoins que chez les boulangers (tableau IX).

Tableau VIII

RAST : résultats positifs en fonction des symptômes chez les boulangers.

Allergènes	Asympt. n = 15		Rhino-conj. n = 8		Asthme n = 3	
	n	%	n	%	n	%
courants n = 4	1	6,67 %	0	0 %	0	0 %
professionnels n = 7	0	0 %	0	0 %	1	33,3 %
Dt Pt	1	6,67 %	0	0 %	0	0 %
Dt Fa	1	6,67 %	0	0 %	0	0 %

Le TPBS ne produit aucune variation significative du VEMS, du MEF 50, de la capacité synchrone (CS) chez les sujets témoins (tableau X). Parmi les boulangers, 22 sujets asymptomatiques ou avec rhino-conjonctivite ne réagiront pas. Un brioche, sans plainte clinique, présentera une chute du MEF 50 de 37 %, de la capacité synchrone de 22 %, du VEMS de seulement 1 %. Les trois boulangers symptomatiques de rhino-conjonctivite et d'asthme présenteront, endéans 1 à 3 minutes d'exposition, une réaction bronchique caractéristique avec une

Tableau IX
Fonction respiratoire :
Moyenne des valeurs de base.

	Témoins n = 24	Boulangers n = 26
CV (%)	94,91 ($\pm$ 13,3)	95,98 ($\pm$ 10,92)
VEMS (%)	91,74 ($\pm$ 14,13)	91,96 ($\pm$ 10,7)
MEF 50 (%)	82,74 ($\pm$ 28,78)	82,96 ($\pm$ 27,07)
CS (%)	92,39 ($\pm$ 17,54)	95,36 ($\pm$ 17,62)

chute des VEMS et MEF 50 supérieure à 20 %, accompagnée de rhinorrhée et de larmolement, de sibilances à l'auscultation. Une chute de PA fut également mesurée chez 2 d'entre eux. Après observation de la réaction bronchique, ces 3 sujets ont reçu du Fenoterol en inhalation, levant le bronchospasme chez tous. Aucun traitement complémentaire de fut administré. Aucune réaction tardive ne fut signalée.

Tableau X – Moyenne des variations de VEMS, MEF 50 et CS après le TPBS.

	Témoins n = 24	Asympto. n = 15	Rhino-conj. n = 8	Asthme n = 3
Δ VEMS (%)	+ 4 ($\pm$ 1,57)	0 ($\pm$ 0,92)	- 5,3 ($\pm$ 4,85)	- 33 ($\pm$ 2,65)
Δ MEF 50 (%)	- 3 ($\pm$ 3,7)	- 4,5 ($\pm$ 3,66)	- 1,3 ($\pm$ 6,68)	- 59 ($\pm$ 6,24)
Δ CS (%)	+ 1,3 ($\pm$ 3,2)	- 9,3 ($\pm$ 2,57)	+ 4,4 ($\pm$ 4,58)	- 16 ($\pm$ 3,18)

4. *Prélèvement atmosphérique des farines* : ces prélèvements sont échelonnés sur 8 heures de travail. Ils sont réalisés par la sédimentation de la farine en suspension dans l'air sur des lames porte-objets enduites de vaseline déposées à différents points des trois ateliers. Elles sont secondairement colorées au Lugol.

Les endroits les plus riches en farine dans l'air sont le feuilletage et le pétrissage (tableau XI), viennent ensuite la ligne de panification et l'atelier des pains français. Enfin, l'enfournement semble moins exposé et de façon plus constante au cours de la nuit de travail.

6. Conclusion et discussion

Parmi les 26 boulangers étudiés, nous avons recensé 8 cas de rhinite ou conjonctivite, 3 cas d'asthme au contact de la farine.

Tableau XI – Numération des grains de farine recueillis à différents points de fabrication.

Heures	Feuilletage	Pétrissage	Atelier des pains français	Ligne de panification	Enfournement
1	508	338	222	191	300
2	793	774	291	211	406
3	1541	1459	335	300	395
4	Amas de farine	1744	464	393	81
5	-	1946	512	410	210
6	-	Amas de farine	534	529	266
7	-	-	797	Amas de farine	277
8	-	-	Amas de farine	-	298

Chez les boulangers asymptomatiques, la sensibilisation cutanée et les IgE spécifiques pour les allergènes courants sont comparables aux valeurs absorbées dans la population générale non exposée professionnellement. Concernant les allergènes professionnels, farine et/ou grains de céréale, on n'observe pas de réponse positive (supérieure à 2) aux tests cutanés et au RAST. Aucune réaction ne fait suite aux tests de provocation bronchique spécifique dans cette population asymptomatique, soulignant la haute spécificité de ce test par l'absence de faux positif.

Parmi les boulangers signalant de la rhinite et/ou conjonctivite, on ne relève aucune réponse positive (supérieure à 2) aux tests cutanés et au RAST pour aucun allergène. On observe, comme dans la population asymptomatique, quelques réactions douteuses (score 1 ou 2) pour des allergènes courants ou professionnels. Ces constatations nous permettent d'envisager l'origine probablement irritative des rhinites évoquées dans ce cas. L'évolution de ces symptômes est toutefois à suivre de même que le devenir des sujets présentant des tests douteux pour les allergènes professionnels. Aucune réaction ne sera observée, ici non plus, après tests de provocation bronchique spécifique.

Pour les 3 boulangers avec asthme apparaissant au contact de la farine, ils présentent tous au moins un test cutané positif aux grains et farines de froment ou de seigle. L'orge, l'avoine et le riz restent douteux à négatifs, ces allergènes ne semblent rien apporter au diagnostic de farinose. Les IgE spécifiques aux céréales n'atteignent pas souvent le score de 3 (un seul cas). Les scores 1 et 2 doivent donc être pris en compte dans la recherche étiologique de l'asthme des boulangers. Par ailleurs, un score de 0 n'exclut pas l'origine allergique des symptômes. Cette dernière constatation est valable également pour les dosages des éosinophiles sanguins et des IgE totales : les valeurs normales n'excluant pas l'allergie. Le test de provocation bronchique spécifique fut positif chez ces 3 boulangers avec apparition immédiate de rhinite et objectivation d'un syndrome obstructif sévère. Deux d'entre eux présentèrent également une

chute de PA, ces symptômes furent rapidement réversibles sous traitement. Nous soulignerons donc l'intérêt de tests cutanés présentant une plus grande sensibilité que le RAST. Ils sont par ailleurs moins coûteux mais nécessitent plus de temps pour leur réalisation. Le test de provocation bronchique à la farine apparaît hautement spécifique dans le diagnostic d'asthme faisant suite à l'exposition à ces pneumallergènes, il n'est cependant pas dénué de risque.

Concernant les contaminants de la farine étudiés à l'aide des tests cutanés (dermatophagoides farinae et Tribolium Confusum), la sensibilisation n'est pas supérieure chez les boulangers par rapport au groupe témoin. Lorsqu'une réaction cutanée est présente, elle apparaît sans relation avec les symptômes et est toujours corrélée avec un test positif aux dermatophagoides pteronyssinus. Le dosage d'IgE spécifiques aux dermatophagoides farinae en comparaison avec les dermatophagoides pteronyssinus est par

contre plus fréquemment augmenté chez les boulangers, les scores restant toutefois douteux d'ordre 1 et 2, alors que les IgE spécifiques sont négatives pour les dermatophagoides pteronyssinus. A nouveau, le plus souvent ces valeurs ne sont pas corrélées avec les symptômes mais bien avec les tests cutanés.

Ces contaminants de la farine ne semblent donc pas jouer de rôle dans l'origine des symptômes évoqués dans la population étudiée ici.

REMERCIEMENTS

Nous remercions Monsieur KREUSCH, Directeur de l'entreprise qui nous a permis de réaliser cette étude, la société PHARMACIA pour les dosages d'IgE totales et spécifiques, Messieurs HEULENS et VAN DE WEYER du F.M.P. pour les renseignements fournis.

Tableau XII
Résumé des différentes données.

Témoins							Boulangers						
Sujets	Anamnèse R, C, A*	Tests cutanés > 2 (Farines et ou grains)	Eosino > 6 %	IgE totales 200 U/ml	Rast > 2 grains	TPBS* farine	Sujets	Anamnèse R, C, A*	Tests cutanés > 2 (Farines et/ou grains)	Eosino > 6 %	IgE totales 200 U/ml	Rast > 2 grains	TPBS* farine
1.				+			1.						
2.							2.						
3.							3.	R					
4.							4.						
5.							5.						
6.							6.	R, C, + A	+				+
7.							7.	R					
8.							8.	R, C, + A	+				+
9.							9.	R					
10.		+	+			±	10.						
11.							11.	R					
12.							12.						
13.							13.	R					
14.							14.	C					
15.				+			15.						
16.							16.						±
17.							17.	R, C, + A	+		+	+	+
18.							18.						
19.							19.						
20.							20.						
21.							21.						
22.							22.						
23.							23.						
24.							24.				+		
							25.	R					
							26.	R					

* R : rhinite, C : conjonctivite, A : asthme.

* Test de provocation bronchique spécifique

REFERENCES

- BAUR N., DORSCH W., VON LIEBE V. — Comparison between Rast, skin test and inhalational provocation tests in patients with baker's asthma and fungal asthma. *Z-Hautkr* 54.7, 301-305, 1979.
- BALDO B.A., KRILIS S., WRIGLEY C. W. — Hypersensitivity to inhaled flour allergens. *Clinical allergy* 35, 45-56, 1980.
- BLOCK G., TSE S. K., KIEK K., CHAN H. et CHAN, YEUNG H. — Baker's asthma. *Clinical allergy* 13, 359-370, 1983.
- CHARPIN J. — *Allergologie*, 2^e Edition Flammarion, 743, 748, 1986.
- CHIDA K., SATO A., MONDA K., et coll. — A case of chronic hypersensitivity pneumonitis induced by wheat flour. *JPN-J. Thorac — Dis* 23/12, 1472-1479, 1988.
- DEBELIC M., SARVAN B. — Occupational flour allergy : baker's asthma and rhinitis. *Prax — Klin — pneumol* 36/9, 389-392, 1982.
- DROUET M., SABBAH A., Le SELLIN J., BONNEAU J.-C. — Pollinosis and allergy to wheat flour in the digestive tract. *Allerg — Immunol* 17/9, 509-512, 1985.
- HARTMANN A.L., WURTRICH R., DEFLOREN — STOLZ R. et coll. — Atopy screening : Prick — multitest, total IgE or RAST ? *Schweiz Medical Wochenschr* 115/14, 466-475, 1975.
- HEINE A., FOX G. — Baker's eczema through chromium compound in flour. *Derm-Beruf-Umwelt* 28/4, 113-115, 1980.
- HERXHEIMER H. — The skin sensitivity to flour of baker's apprentices. A final report of a long term investigation. *Acta-allergologica* 28/1, 42-49, 1973.
- HEYER N. — Baking additives as occupational allergens in professions working with flour. *Allergologie* 6/10, 389-392, 1983.
- KENTNER M., HARTUNG M. — The mode of action and uses of disodium cromoglycate in the treatment of obstructive respiratory disorders with special reference to occupation — induced asthma. *Prax — Klin — Pneumol* 36/7, 318-322, 1982.
- KENTNER M., HARTUNG M., THURAU J., KOSTLER CH. — The value of immunological and inhalation challenge tests in the diagnosis of occupational flour allergies of the respiratory system. *Prax — Klin — Pneumol* 36/4, 183-189, 1982.
- LOSCHIAVO S. R. — 4' (3,3 — dimethyl — 1 — triazeno) acetanilide to protect packaged cereal against stored products insects. *Food technology* 23/4, 181-185, 1970.
- MAGIS N. — Aperçu de l'histoire naturelle des complexes d'espèces du genre *Tribolium*. *Inst. royal des sciences naturelles de Belgique* 30/25, 1954.
- MEYER W.-C. Prognosis of occupational bronchial asthma after change of occupation and elimination of antigen. *Munchmedwtschr* 119/11, 363-366, 1977.
- MORICHEAU-BEAUCHANT G., BRISON J., DAJEAN E., VALLETTE J. — Importance relative de l'allergie à l'éphedrine. *Revue Française d'allergologie* 4, 260, 1964.
- NAKAZAWA T., TOYOTA T., FURUKAWA M. et coll. — Inhibitory effects of various drugs on dual asthmatic responses in wheat flour sensitive subjects. *All-Clin — Immunol*, 1-9, 1976.
- NEWELL E., GOO D. — The flour beetles of the genus *tribolium*. U.S. departement of agriculture, Washington D.C., *Technic bulletin* 498/3, 1936.
- POPA V., GAVANESCA G. et O. — Occupational and non-occupational respiratory allergy in bakers. *Acta allergologica* 29, 159-177, 1970.
- PRICHARD M.G., RYAN G., MUSK A.W. — Wheat flour sensitisation and airways disease in urban bakers. *British journal in med* 41/4, 450-454, 1984.
- PUGLIESE S., CORSICO R. — Disodium cromoglycate in the treatment of occupational allergic asthma induced by flour. *Lavumano* 25/3, 76-83, 1973.
- SCHULTZE-WERNINGHAUS G., SCHWARTING H.M. — Effect of cromoglycate on allergen inhalation tests in occupational asthma in bakers. *Pneumologie* 15/12, 115-126, 1974.
- SUTTON R., SKERRITT J.M., BALDO B.A., WRIGLEY C.W. — The diversity of allergens involved in baker's asthma. *Clinical allergy* 14, 93-107, 1984.
- THIEL H. — Baker's asthma : epidemiological and clinical findings; needs for prospective studies. *Prax — Klin — Pneumol* 37/spec. 1, 774-780, 1983.
- THIEL H. — Occupationally induced obstructive airway diseases : respiratory allergies of the immediate type. *Atenweg — lungenkrakt*, 11/7, 297-302, 1985.
- TRIEBIG G., THURAU J., ZOBEL A., WELTLE D. — Allergen inhalation test, acetylcholine tests and RAST as criterias for the assessment of an occupational caused obstructive airway disease. *Arbeit-Sozial — Preventiv Med* 14/10, 232-235, 1970.
- WRAITH D.-G., CUNNINGTON A.M., SEYMOUR W.H. — The role and allergenic importance of storage mites in house dust and other environments. *Clinical allergy* 9, 545-561, 1979.
- WOTOWITZ H.J. — Baker's disease. *Atenwegs. — lungenkrakt* 11/11, 493-499, 1985.

Bean Hypersensitivity in Coffee 'Workers' Asthma: A Clinical and 'Immunological Appraisal

Presented by Samuel B. Lehrer, Ph.D.

More than 20 million people are employed by the coffee industry. The United States is the major importer of coffee. Recent years have seen a gradual decline in the number of coffee manufacturers and employees in the United States because of consolidation trends and increasing mechanization. In 1982, there were 150 coffee companies in the United States with a total of 11,800 workers.

Numerous reports of allergic reactions among coffee workers were made in the 1950s and 1960s. Coffee industry workers develop occupational asthma, rhinitis, or dermatitis. The nature of coffee bean allergen was conflictingly reported to be chlorogenic acid in green coffee beans or protein in castor and green coffee beans by different investigators in the early 1960s. Lehrer noted that the role of chlorogenic acid as an allergen now is doubtful.

During the last 20 years, there have been nine reports of occupational allergic reactions in the coffee industry, exclusively in coffee workers during manufacturing rather than in growers. Most of these cited the green coffee bean or the castor bean as the causative agent. Symptoms included wheezing and shortness of breath, rhinitis, and conjunctivitis.

Lehrer presented data from his studies of coffee workers. The symptomatic coffee workers had positive skin test reactions to extracts of green coffee bean and coffee dust. The asymptomatic coffee workers and the control group did not demonstrate sensitivity by skin testing.

The hypothesis that coffee allergen was active in sensitive individuals was supported by the fact that specific IgE antibodies were detected in the serum of symptomatic workers that were not present in the other groups.

A study of two coffee manufacturing plants was conducted. Coffee dust concentrations were measured in milligrams per cubic meter. No significant difference in quantity was found among the three work areas—the green coffee bean area, the mixed area, and the roasted coffee bean area. However, a qualitative difference was suspected. A study that tested mice with various extracts found that coffee dust and green coffee beans contained potent allergens. Castor bean and green coffee bean demonstrated no cross-reactivity in this animal model.

An epidemiologic survey was conducted for the prevalence of pulmonary symptoms, atopic disease, x-ray and pulmonary function abnormalities, and skin tests. A standardized questionnaire, chest x-rays, and skin tests were conducted in 372 workers. Skin testing detected 11 to 15% atopic individuals among the subjects. Lower respiratory symptoms, including wheezing and coughing, were reported in 32 to 37%. Upper respiratory symptoms, such as hayfever or sinus problems, were reported in 42 to 43%. Chronic bronchitis was found in 3 to 7%. Occupational asthma was not found in the two plants studied. Symptom prevalence did not differ significantly among various exposure areas. Only the castor bean radioallergosorbent test (RAST) test was significant to the exposure area, with the highest positive reactions among workers in the green coffee bean exposure area.

Thus, castor bean appears to be the most potent

Research Professor of Medicine, Tulane Medical Center

allergen, because the greatest number of coffee workers had hypersensitivity responses to it. RAST inhibition studies of extracts of sack samples support the hypothesis that coffee workers are exposed to castor bean allergen through handling contaminated sacks.

In conclusion, Lehrer noted that the potential for occupational exposure to allergens in the coffee industry is considerably lower than in other industries that are less mechanized.

REFERENCES

1. Coffee—The World Cup. Prepared by the promotion fund of the International Coffee Organization. Samuel E. Stravisky and Associates, Inc. Public Relations International, Washington, DC.
2. Bernton HS. Occupational sensitization—a hazard to the coffee industry. *JAMA* 223:1146–1147, 1973.
3. Karr RM, Lehrer SB, Butcher BT, Salvaggio JE. Coffee workers asthma: a clinical appraisal using the radioallergosorbent test. *J Allergy Clin Immunol* 62:143–148, 1978.
4. Jones RN, Hughes JM, Lehrer SB, et al. Lung function consequences of exposure and hypersensitivity in workers who process green coffee beans. *Am Rev Respir Dis* 125:199–202, 1982.
5. Zuskind E, Kanceljak B, Skuric Z, Butkovic D. Bronchial reactivity in green coffee exposure. *Br J Ind Med* 42:415–20, 1985.
6. Van Toom DW. Coffee workers lung. A new example of extrinsic allergic alveolitis. *Thorax* 25:399–405, 1970.
7. Vanderbosch JM, Van Toom DW, Wagenaar SS. Coffee workers lung: reconsideration of a case report. *Thorax* 38:720, 1983.
8. Freedman SO, Siddiqi QI, Krupay J, Schon AH. Identification of a simple chemical compound (chlorogenic acid) as an allergen in plant materials causing human atopic disease. *Trans Assoc Am Physicians* 75:99–106, 1962.
9. Layton LL, Green FC, Corse JW, Panzani R. Pure chlorogenic acid not allergenic in atopy to green coffee: a specific protein probably is involved. *Nature* 203:188–189, 1964.
10. Layton LL, Green FC, Panzani R. Allergy to green coffee: failure of patients allergic to green coffee to react to chlorogenic acid, roasted coffee or orange. *J Allergy Clin Immunol* 36:84–91, 1965.
11. Figley KD, Rawlings FFA. Castor bean: an industrial hazard as a contaminant of green coffee dust and used burlap bags. *J Allergy Clin Immunol* 21:545–553, 1950. □

Hypersensitivity Reactions in Seafood Workers

Presented by Samuel B Lehrer, Ph.D.

Seafood is a major industry in the United States, employing a total of 350,000 workers as of 1986. In view of the known allergenicity of seafood in consumers, the large number of allergic reactions reported among seafood workers is not surprising. Allergenic agents include snowcrabs, shrimp, oysters, shell products, rubber boots, and fishing nets. Allergic reactions have been reported among fishermen, seafood processors, oyster shuckers, caterers, and restaurant chefs.

Allergic reactions to seafood can be divided into two categories: respiratory (including asthma, pulmonary hypersensitivity, and respiratory allergy) and dermatological (including dermatitis, contact urticaria, skin diseases, and eczema). Lehrer explained that this presentation would focus on respiratory reactions, which occur more frequently in seafood workers and have been studied more thoroughly.

A study of snowcrab processing workers examined occupational exposure at two processing plants. Large amounts of steam and water vapor released by the boiling process were seen, and ventilation was insufficient. After cooking and cooling the crabs, workers remove the meat from the legs and claws, thereby becoming exposed to steam, meat, and shell particles. There can be as many as 300 workers in one room.

The purpose of the epidemiologic study was to determine the prevalence of respiratory symptoms, atopic traits, and skin reactivity to snowcrab among the 303 workers. According to the histories obtained, the workers were divided into three groups: 1) no symptoms of respiratory allergy; 2) symptoms of dyspnea and/or cough and phlegm production, but no bronchospasms

and no relationship of symptoms to work; and 3) symptoms of asthma. The latter group was then divided into subgroups, depending on whether their asthma was thought to be related to work exposure (e.g., symptoms occurred mostly at work). The diagnosis of occupational asthma was confirmed in 15.6% of the workforce studied. Of the occupational reactions reported, asthma was reported by 34%, rhinitis and/or conjunctivitis by 18%, and skin rash by 24%. An association between allergic reactions, such as asthma, rhinitis, and skin rash, and positive skin test results was shown.

These results suggested an IgE sensitization to crab in these workers. In 1984, a group of workers was restudied using different snowcrab extracts for skin tests and specific IgE antibody measurements. The results of this study suggested a highly significant relationship between the presence of immediate skin test reactivity, or increased serum IgE antibodies, and the occurrence of occupational asthma. Other studies using the Western blot or immunoprint method have revealed a number of important allergens in snowcrab extracts.

Lehrer also discussed some of his crustacea studies. Although not in an occupational setting, the studies revealed a variety of antigens and allergens present in the extracts and showed that a number of allergens are still present after boiling. In addition, significant cross-reactivity was found among shrimp, crawfish, crab, and lobster antigens. Following boiling, the fluid was found to contain equal or greater amounts of antigen as the seafood meat.

In contrast to coffee industry workers, little is known about allergic reactions among seafood workers because of an insufficient number of studies, Lehrer concluded. The seafood industry has been difficult to study for a number of reasons; for example, smaller plant sizes and seasonal operations make access for researchers more difficult.

Research Professor of Medicine, Tulane Medical Center

REFERENCES

1. O'Baunon BK, ed. Fisheries of the United States. 1987. U.S. Department of Commerce.
2. May CD, Boek SA. A modern clinical approach to food hypersensitivity. *Allergy* 33:166-188, 1978.
3. Cietie J, Legge JS, Friend JA, Reid TM. Pulmonary hypersensitivity in prawn workers. *Lancet* 8208-9, 1350-1353, 1980.
4. Carino M, Elia G, Molinini R, Nuzzaco A, Androsi L. Shrimp-meal asthma in the aquaculture industry. *Med Lav* 76:471-475, 1985.
5. Hjorth N, Roed-Peterson J. Occupational protein contact dermatitis in food handlers. *Contact Derm* 2:38-42, 1976.
6. Beck HL, Nissen BK. Contact urticaria to commercial fish in atopic persons. *Acta Derm Venereol (Stockh)* 63:257-260, 1983.
7. Cartier A, Malo JL, Forest F, et al. Occupational asthma in snow crab processing workers. *J Allergy Clin Immunol* 74:261-269, 1984.
8. Cartier A, Malo JL, Ghezzi H, McCants M, Lehrer SB. IgE sensitization in snow crab processing workers. *J Allergy Clin Immunol* 78:344-348, 1986.
9. Bush RK, Meier-Davis S, Lehrer SB, Cartier A. Snow crab asthma: identification of allergens by immunoblotting. Submitted for publication.
10. Lehrer SB. The complex nature of food allergens: studies of cross-reacting crustacea allergens. *Ann Allergy* 57:267-272, 1986.
11. Halmeupuro L, Salvaggio J, Lehrer SB. Studies of allergens present in crawfish and lobsters. *Int Arch Allergy Appl Immunol (Basel)* 84:165-172, 1987. □

L'asthme professionnel:

Rapport du comité spécial de la Société de thoracologie du Canada

par Jean-Luc Malo, m.d.

De plus en plus de travailleurs entrent en contact avec des substances qui causent de l'asthme professionnel. Cette situation a des répercussions sociales et économiques significatives. La Société de thoracologie du Canada (section médicale de l'Association pulmonaire du Canada) s'y est intéressée.

L'asthme professionnel est une cause de déficit fonctionnel respiratoire de plus en plus fréquente. On attribue l'accroissement de son incidence et de sa prévalence à une utilisation plus répandue des agents étiologiques, à l'augmentation du nombre de ces agents et à de meilleures méthodes diagnostiques. On estime aujourd'hui qu'il existe environ 120 causes possibles d'asthme professionnel.

La maladie est source de nouveaux problèmes pour les autorités canadiennes de santé et de sécurité responsables de la prévention des maladies professionnelles et pour les commissions de la santé et de

la sécurité du travail dont le mandat comprend la réduction des conséquences financières et sociales des maladies professionnelles. La Société de thoracologie du Canada (section médicale de l'Association pulmonaire du Canada) a établi des recommandations destinées aux responsables qui allouent des compensations aux travailleurs atteints de maladies professionnelles (voir "Recommandations de la Société de thoracologie du Canada" p. 58). La Société a également dressé une liste de problèmes reliés à l'asthme professionnel que des études devront éclaircir (voir "Besoins de recherche" p. 63).

Obstruction des voies aériennes en milieu de travail

Les conditions respiratoires caractérisées par de l'obstruction bronchique peuvent être produites sur les lieux du travail par l'exposition à des poussières, des émanations ou des gaz. L'obstruction des voies aériennes peut être variable

(asthme) ou fixe (obstruction chronique des voies aériennes).

La définition de l'asthme proposée par le comité conjoint de l'American Thoracic Society et de l'American College of Chest Physicians est généralement acceptée: "L'asthme est une condition caractérisée par une hyperexcitabilité de la trachée et des bronches à des stimuli variés et se manifestant par un rétrécissement diffus des voies aériennes qui varie en gravité soit spontanément soit suite à un traitement."

On a décrit quatre conditions caractérisées par l'obstruction des voies aériennes. Pour chacune de ces conditions, la variabilité du calibre bronchique est reconnue et l'on retrouve une hyperexcitabilité bronchique suite à l'exposition aux poussières, aux émanations et aux gaz dans le milieu de travail. Il s'agit de:

- L'asthme professionnel dû à la sensibilisation à des substances spécifiques;
- La byssinose due à l'exposition au coton et au lin, entre autres;
- Le Reactive Airways Dysfunction Syndrome (RADS) dû à l'exposition intense à des substances toxiques;
- L'obstruction bronchique variable due à l'exposition à des substances irritantes non spécifiques.

Ce rapport se limite à l'asthme professionnel, une condition récem-

Dr MALO est professeur agrégé, faculté de médecine de l'Université de Montréal, et pneumologue, Hôpital du Sacré-Coeur, Montréal.

Ont également participé à la rédaction du Rapport les docteurs L.P. Boulet, J. Broder, A. Cartier, M. Chan-Yeung, D. Cockcroft, F.E. Hargreave, W.K.C. Morgan, S. Tarlo et P. Warren (président).

L'asthme professionnel est une obstruction variable des voies aériennes causée par une substance sensibilisante rencontrée sur les lieux du travail.

Recommandations

Que le terme "asthme professionnel" soit réservé à une obstruction des voies aériennes variable accompagnée d'hyperexcitabilité bronchique due à une sensibilisation à une substance rencontrée spécifiquement au travail.

Que les responsables de la santé et de la sécurité professionnelles identifient à travers le pays les médecins considérés comme des experts dans le diagnostic et l'évaluation de l'asthme professionnel. Des centres régionaux d'expertise pourraient être établis.

Que les responsables de la santé et la sécurité au travail au Canada identifient les industries qui exposent des travailleurs à des causes connues d'asthme professionnel et les informent des risques de la maladie.

Que les commissions de santé et de sécurité du travail au Canada acceptent la nature de l'asthme professionnel et développent des échelles d'invalidité qui sont vraiment applicables à l'asthme professionnel, tel que recommandé dans ce rapport. Ces commissions devraient obtenir l'expertise de membres ou de consultants aptes à diagnostiquer et à traiter l'asthme professionnel.

Que les travailleurs chez lesquels on soupçonne la présence d'asthme professionnel soient référés à des experts régionaux. Un diagnostic objectif d'asthme doit être établi et le lien de l'asthme avec l'exposition à l'agent responsable sur les lieux du travail doit être confirmé avant que le travailleur ne soit avisé de quitter ce travail. Si nécessaire, pour confirmer le lien entre l'exposition à l'agent responsable sur les lieux du travail et l'asthme, les commissions de santé et de sécurité du travail devraient permettre aux travailleurs de recevoir des prestations pour les périodes d'absence au travail. (Ces périodes sont nécessaires pour déterminer si l'amélioration des symptômes de l'asthme est suivie d'une récurrence au retour au travail.)

Que le diagnostic d'asthme professionnel dépende de la corrélation des changements de l'obstruction bronchique et de l'hyperexcitabilité bronchique avec une exposition variable à la cause. Les tests de provocation en laboratoire pour prouver les causes d'asthme professionnel ne font plus partie de l'investigation habituelle.

Que l'évaluation du déficit fonctionnel et de l'invalidité pour les travailleurs atteints d'asthme professionnel inclue une mesure de l'hyperexcitabilité bronchique. Les échelles d'invalidité doivent tenir compte de la fonction pulmonaire de base, de l'hyperexcitabilité bronchique et du besoin en médicaments du travailleur. La médication est évaluée par la quantité minimale nécessaire pour soulager les symptômes de façon régulière sur une période d'un mois. Les échelles de base sont fondées sur la gravité de l'obstruction bronchique avant bronchodilatateur (le VEMS). Ces mesures sont modifiées par le degré de l'hyperexcitabilité bronchique et le besoin en médication.

Le déficit fonctionnel et l'invalidité doivent être évalués tous les deux ans avant que l'on décide de leur permanence.

Une procédure devrait être instaurée pour diagnostiquer et évaluer le travailleur atteint d'asthme professionnel de sorte que des décisions de compensation puissent être prises rapidement et que le travailleur puisse réintégrer le marché du travail aussi tôt que possible.

ment reconnue par la communauté scientifique médicale et qui pose de nouveaux problèmes pour les services professionnels de santé et les comités de compensation financière.

La *byssinose* est une condition bien établie. Les médecins oeuvrant dans le domaine des maladies professionnelles et les comités de compensation traitent souvent cette affection. Des mesures préventives ont été instituées dans les industries du coton et du lin.

Le *RADS* a été rapporté seulement par un auteur. L'obstruction aiguë post-inflammatoire des voies aériennes après une exposition à des concentrations toxiques de produits chimiques comme le chlore, le fluor, les acides forts, l'oxyde sulfureux, l'oxyde nitreux, l'ammoniaque et des solvants était connue antérieurement. Cependant, la reconnaissance d'une hyperexcitabilité bronchique chez ces sujets est plus récente. La fréquence de cet état, son histoire naturelle et le degré de déficit fonctionnel qu'elle engendre n'ont pas été établis.

L'*obstruction variable* des voies aériennes due à une exposition à des irritants est répertoriée dans les mises à jour sur l'asthme mais sa nature n'a pas été établie. Les causes incluses dans ces listes sont le SO₂, l'ozone, entre autres agents. Ces agents ne sont ni sensibilisants ni allergéniques. Ils agissent par

voie d'une bronchoconstriction réflexe et le relâchement direct de médiateurs. Cette condition est probablement associée à une exposition chronique au produit irritant au-delà de ce que l'on désigne comme le Threshold Limit Value (TLV). Le rôle d'une hyperexcitabilité bronchique préexistante dans la réponse aux irritants n'est pas clair, mais elle pourrait y contribuer directement. L'interaction avec le tabagisme et des conditions pulmonaires pré-existantes ainsi que l'histoire naturelle de l'obstruction bronchique due à des irritants n'ont pas été établies.

La compensation pour byssinose est acceptée. Le RADS et l'obstruction spécifique variable due à des irritants sur les lieux du travail restent trop vagues pour faire l'objet de recommandations spécifiques. La nécessité d'une compensation doit être décidée après l'analyse individuelle des cas. L'aggravation de l'asthme par des causes non sensibilisantes devrait être compensée seulement si des niveaux excessifs de l'agent causal sont présents.

Définition

L'asthme professionnel est une obstruction variable des voies aériennes causée par une substance présente sur les lieux du travail. La substance causale a sensibilisé la personne au travail. Bien que la substance sensibilisante puisse ne

pas être spécifiquement identifiée, ses effets peuvent être démontrés. Pour des substances de grand poids moléculaire, la sensibilisation a habituellement une base immunologique, médiée par les immunoglobulines E (IgE), mais la base de la sensibilisation aux substances de faible poids moléculaire demeure incertaine.

Causes

Un grand nombre de substances pouvant causer l'asthme ont été identifiées. Certaines l'ont été grâce à des données épidémiologiques et à des tests de provocation bronchique, d'autres grâce à des rapports de cas cliniques. Une liste de références pour ces agents est disponible sur demande. Le tableau 1 présente une liste des causes d'asthme professionnel.

Les seules causes qui devraient être considérées comme confirmées sont celles dont on a prouvé l'effet sur l'hyperexcitabilité bronchique et l'obstruction des voies aériennes. Les autres substances devraient être considérées comme des causes possibles d'asthme professionnel.

Quand une substance répertoriée est soupçonnée dans un cas d'asthme professionnel, les documents pertinents devraient être étudiés afin de déterminer s'il s'agit d'une cause reconnue. La liste des agents déclencheurs

Des symptômes qui s'aggravent en soirée et durant les jours de travail, mais diminuent au cours de la fin de semaine ou en période de vacances suggèrent que l'asthme est relié au travail.

Besoins de recherche

Établissement ou rejet des causes possibles d'asthme professionnel

Détermination de la prévalence et de l'incidence de l'asthme professionnel chez des travailleurs exposés à des causes connues.

Détermination que différents types d'exposition et que l'exécution de tâches différentes produisent de l'asthme au même degré.

Examen de la relation entre les changements d'hyperexcitabilité bronchique à des agents spécifiques et non spécifiques tels que les poussières inertes, les émanations et l'air froid.

Meilleure définition du "Reactive Airways Disease Syndrome" et de l'obstruction bronchique secondaire à l'exposition chronique à des irritants.

Évaluation des conséquences du diagnostic précoce de l'asthme professionnel et du retrait précoce d'un travailleur à l'exposition à l'agent responsable de son affection

Établissement et évaluation prospective d'échelles d'invalidité chez les travailleurs.

Identification des facteurs de risque personnels qui contribuent au développement de l'asthme professionnel.

Élucidation des mécanismes de sensibilisation, particulièrement aux agents de faible poids moléculaire.

Établissement de méthodes de contrôle de l'environnement qui préviendraient l'asthme professionnel.

Évaluation du dépistage médical avant l'embauche et du dépistage périodique qui pourraient contribuer au contrôle de l'asthme professionnel et au développement de méthodes de prévention.

devrait être utilisée par des médecins connaissant le problème, des comités de santé et de sécurité et d'autres intervenants intéressés à l'évaluation de l'asthme en tant que maladie professionnelle. Cette liste ne doit pas être utilisée pour établir un diagnostic d'asthme professionnel chez un travailleur qui développe un trouble respiratoire et est exposé à une substance qui se trouve sur la liste. Le médecin doit confirmer le diagnostic sur une base individuelle et selon les étapes recommandées. Il ne doit

pas présumer que le sujet présente de l'asthme professionnel par exposition à un agent causal présent sur la liste.

Diagnostic

Le diagnostic de l'asthme professionnel doit être établi aussi rigoureusement que celui des pneumocoques traditionnelles. Cependant, les procédures diagnostiques sont différentes de celles des pneumocoques. Chez ces dernières, les causes environnementales sont connues et peuvent être surveillées

dans le milieu de travail, des changements radiologiques se produisent, le lavage bronchoalvéolaire et les biopsies pulmonaires sont disponibles et les changements de la fonction pulmonaire sont constants ou progressent lentement.

Dans l'asthme professionnel, les causes sont multiples, l'environnement de travail est moins bien défini, il n'existe pas de changements radiologiques et la fonction pulmonaire est variable.

Les autorités provinciales responsables de la santé et de la sécu-

L'évidence objective est essentielle au diagnostic de l'asthme professionnel. Elle peut être obtenue par la corrélation des changements d'hyperexcitabilité bronchique et d'obstruction bronchique lors de l'exposition à une substance suspecte au travail.

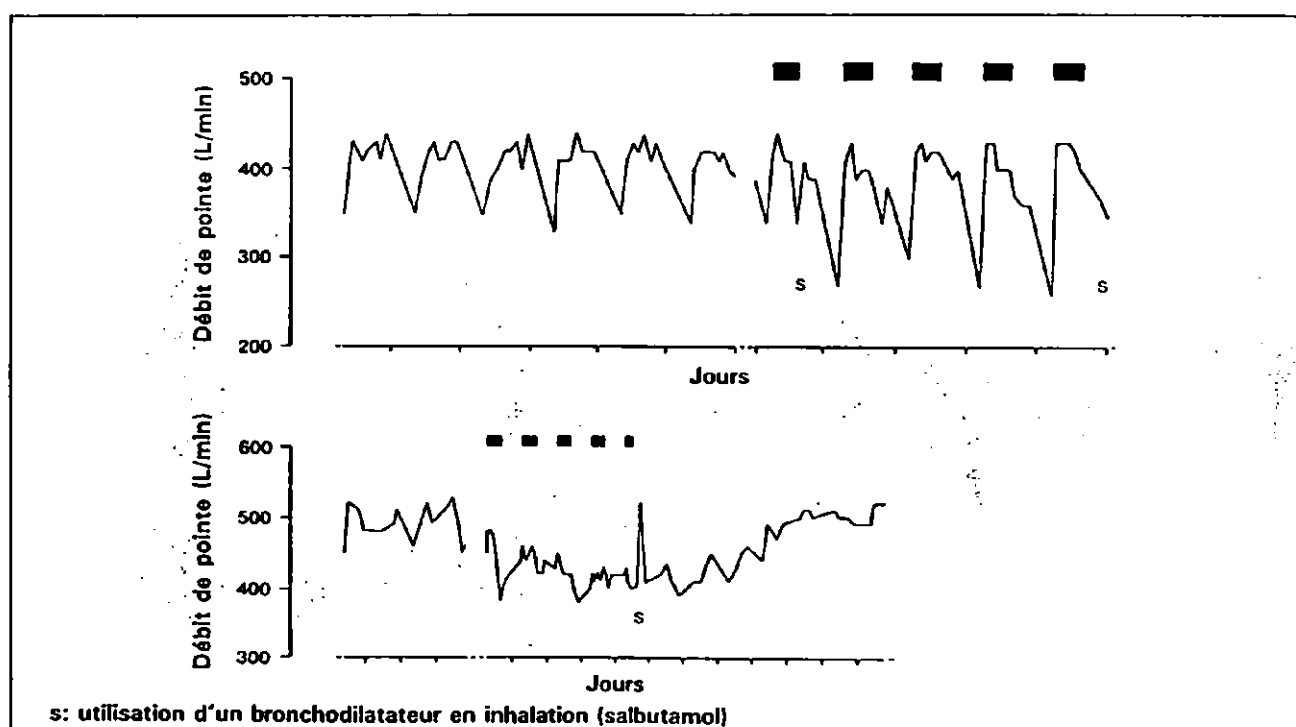


Figure 1. Le graphique du haut illustre une augmentation des variations quotidiennes du débit de pointe. Celui du bas montre une détérioration progressive des valeurs lors d'une période au travail avec une amélioration progressive par la suite. Les rectangles noirs représentent les journées au travail

rité au travail devraient encourager le développement de centres de diagnostic dans les régions appropriées où des médecins et du personnel connaissant tous les aspects de l'asthme professionnel seraient disponibles. Les travailleurs chez qui on soupçonne de l'asthme professionnel devraient être vus dans ces centres aussitôt que possible avant qu'une décision de changement de travail ne soit prise.

La première étape consiste à diagnostiquer l'asthme. Bien que l'histoire de dyspnée intermittente et sibilante suggère fortement l'asthme, le diagnostic devrait être confirmé par des données objectives. Le sujet doit subir des tests de fonction pulmonaire. L'asthme est caractérisé par une obstruction bronchique qui est réversible à un degré significatif lors du traitement ou après un certain temps. L'asthme n'est pas exclu par des

résultats de tests de fonction pulmonaire normaux puisqu'il peut être en rémission. Dans ce cas, l'hyperexcitabilité bronchique non allergénique peut être décelée en utilisant la nébulisation de méthacholine ou d'histamine, l'hyperventilation d'air froid ou des tests à l'exercice. L'hyperexcitabilité bronchique peut diminuer en l'absence d'une exposition à l'agent responsable, mais réapparaître après le retour au travail.

La preuve qu'une substance a produit la sensibilisation et causé l'asthme est obtenue en laboratoire par des tests d'inhalation avec cette substance et une substance de contrôle appropriée.

Tableau - 1

Causes d'asthme professionnel

Animaux

Mammifères (vaches, cochons d'Inde, chevaux, souris, cochons, lapins, rats, moutons)
Oiseaux (poules, acariens des poulaiers, perroquets, pigeons)
Crustacés (crabe des neiges, daphnies séchées, crevettes)
Arthropodes (acariens du pommier, lépidoptères de l'abeille, cochenilles, blattes, grillons, acariens de stockage, lépidoptères du sapin Douglas, chardonneret, vers de la mouche, mouches de mai, vers, chardonneret de la rive mexicaine, mites/papillons, ver à soie, mouche du ver tire bouchon)
Invertébrés (moules, coquilles de perles et d'huîtres, éponges)

Plantes

Aliments (sarrasin, noix, cannelle, graines de café, ail, poussières de grain, farine de grain, houblon, maïs, graines de soja, pollen de fraise, betterave à sucre, fruit du tamarinier, poussière de thé, feuille de tabac)
Gommes (gomme acacia, gomme tragacanth)

Bois

Abirukana	Tanganyika anigni	Buis d'Afrique du sud
Bois du zèbre d'Afrique	Erable d'Afrique	Cèdre rouge de l'ouest
Cèdre du Liban	Cèdre rouge de Californie	
Cocobolla	Noyer de l'Amérique Centrale	
Kejaal	Cèdre blanc de l'est	
Lanau	Iroko	
Magnolia	Acajou	
Chêne	Mûrier	
Ramin	Quillaja	

Fleurs

Soupir de bébé
Chrysanthème

Enzymes biologiques

Enzyme du *Bacillus subtilis* broméline, flaviastase
Enzymes pancréatiques (la papaine, la pepsine)

Moisissures

Alternaria	Aspergillus
Amylase fongique	Produits nourriciers fongiques
Champignons des champs de grains	Spores de champignons

Humidificateurs avec eau contaminée

Amibes
Moisissures (non confirmé)

Flux de soudure

Aminoéthyl éthanolamine
Résine de colophane
Alcool glycol polypropylique

Durcisseurs contenant des catalyseurs

Anhydrides (phthalique, tétraclorophthalique, trémilitique)
Azodicarbonamide
Diméthyl éthanolamine
Diisocyanates (diphénylmétane, hexaméthylène, naphtalène, toluène)

Colorants

Rouge brillant Cibachrome®
Jaune brillant Levafix®
Persulfates et henné

Jaune et bleu brillants Drimaren®
Diamine paraphénylène
Colorant bleu ciel

Métaux

Aluminium (fluorure)
Sels de nickel
Vanadium

Chromates
Sels de platine
Cobalt
Carbure de tungstène

Autres produits chimiques

Chloramine-T
Encre ECG
Fluorure
Fréon
Insecticide organophosphaté
Acide tannique
Urée formaldéhyde

Sels de diazonium
Éthylène diamine
Formaldéhyde
Alcool furfurique (résine de base furan)
Chlorure de polyvinyle
Tétramine triéthylique

Médicaments

Aminophylline
Céphalosporines
Lin
Hexachlorophène
Lycopodium
Pénicillines
Dihydrochlorure de pipérazine
Produits intermédiaires du salbutamol
Chloramines sulphonées

Hydrochlorure d'amprolium
Dichoramine
Poudre de gentiane
Ipecacuanha
Métyldopa
Chlorure d'acide phénylène glycine
Psyllium
Spiramycine
Tétracycline

Il est essentiel que l'évaluation du déficit fonctionnel comprenne une mesure de l'hyperexcitabilité bronchique et la médication nécessaire à l'amélioration de la condition asthmatique.

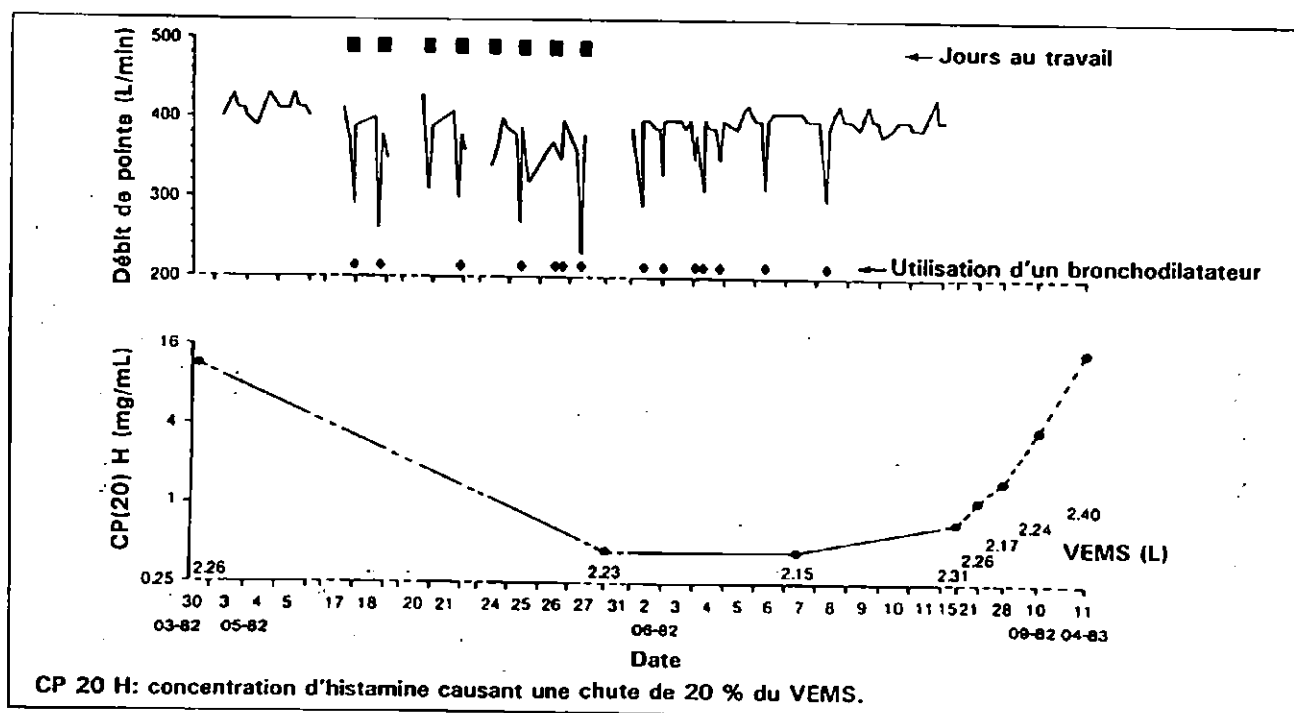


Figure 2. Changements du calibre bronchique et de l'hyperexcitabilité bronchique non allergique (HBNA) suite à l'exposition à un agent sensibilisant.

La deuxième étape consiste à confirmer le lien entre l'asthme et le milieu de travail. Des symptômes qui s'aggravent en soirée et durant les jours de travail, mais qui diminuent au cours de la fin de semaine ou en période de vacances suggèrent que l'asthme est relié au travail.

Toutefois, ces caractéristiques ne suffisent pas pour diagnostiquer l'asthme professionnel ou pour le distinguer de l'asthme exacerbé de

façon non spécifique au travail. La preuve qui supporte le diagnostic est l'enregistrement des symptômes et du besoin en médicaments dans un cahier, couplé avec des mesures de débit de pointe. L'augmentation de la symptomatologie et la diminution des débits de pointe dans l'environnement de travail révèlent une détérioration de l'asthme (figure 1). Cet enregistrement dépend de la précision des observations du travailleur.

L'évidence objective est essentielle au diagnostic de l'asthme professionnel. Elle peut être obtenue par la corrélation des changements d'hyperexcitabilité bronchique et d'obstruction bronchique lors de l'exposition à une substance suspecte au travail (figure 2). Le changement de l'hyperexcitabilité bronchique fournit une preuve objective des effets de l'exposition à l'agent responsable et permet de distinguer l'asthme professionnel de

Quand l'histoire suggère l'asthme professionnel, mais que le monitoring de l'asthme ne le confirme pas par des changements significatifs d'hyperexcitabilité bronchique, le travailleur doit être gardé sous observation.

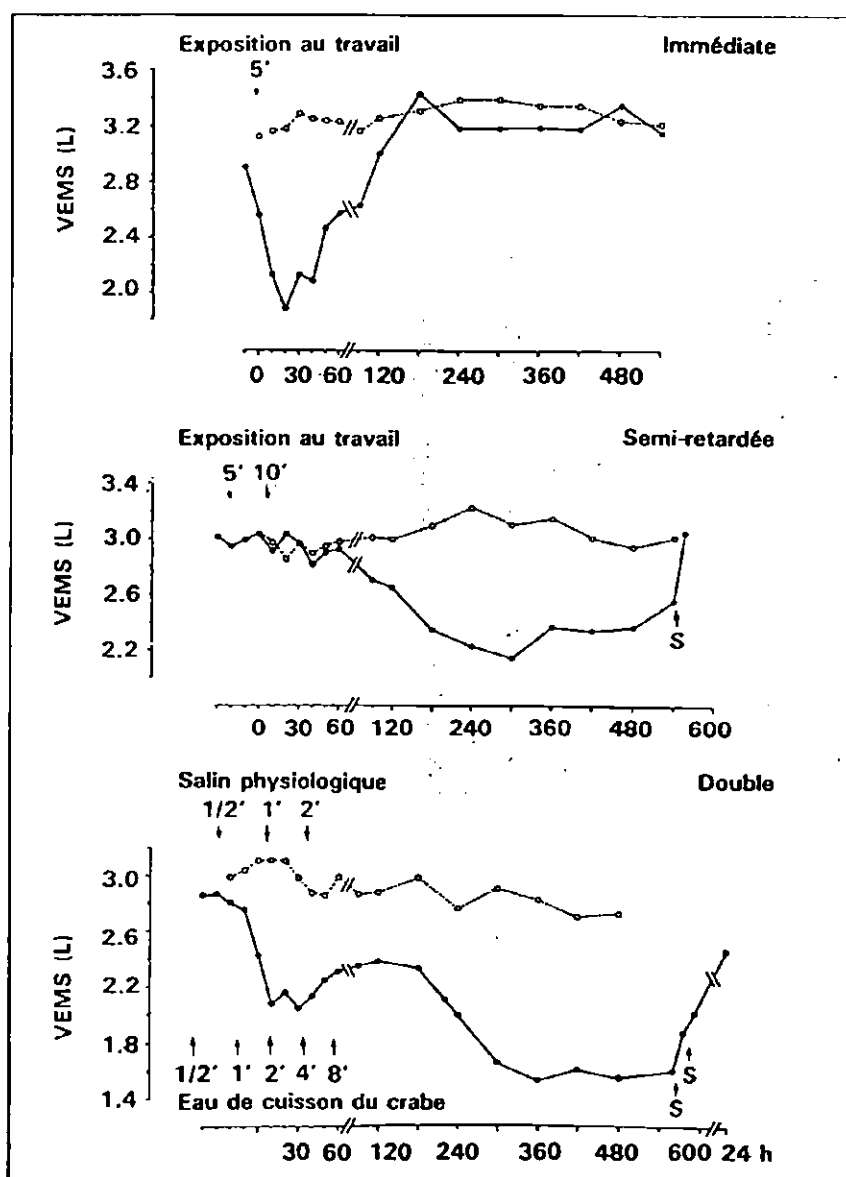


Figure 3. Types de réaction suite à une exposition à un agent sensibilisant.

l'asthme exacerbé de façon non spécifique au travail. Bien que les observations courantes favorisent cette distinction, d'autres recherches sont nécessaires pour la confirmer.

Les autres méthodes utilisées pour mettre en relation l'asthme et le milieu de travail, tel l'enregistrement des valeurs de spirométrie avant et après le quart de travail, ne semblent pas assez spécifiques. De plus, les réactions semi-retardées peuvent ne pas être détectées.

La preuve qu'une substance a produit la sensibilisation et causé l'asthme est obtenue en laboratoire par des tests d'inhalation avec cette substance et une substance de contrôle appropriée (figure 3). Cependant, les tests d'inhalation ne sont pas toujours nécessaires pour confirmer le diagnostic d'asthme professionnel. Les travailleurs exposés à une cause connue d'asthme professionnel et chez lesquels une relation a été démontrée entre des changements de l'obstruction bronchique et l'hyperexcitabilité bronchique d'une part, et l'exposition à l'agent responsable dans le milieu de travail d'autre part, n'ont pas besoin de tests de provocation. Par contre, les tests de provocation sont nécessaires chez les travailleurs dont l'histoire suggère l'asthme professionnel et qui sont exposés à des substances qui

Tableau 2

Échelle de déficit fonctionnel

Valeurs

Obstruction bronchique		Hyperexcitabilité bronchique *		Médication	
Test	Niveau	Test	Niveau	Test	Niveau
VEMS > 80 % pred	0	CP 20 > 8 mg/mL	0	Aucun	0
VEMS de 71 % à 80 % pred	-1	CP 20 de 2 à 8 mg/mL	-1	1 médicament	-1
VEMS de 56 % à 70 % pred	-2	CP 20 de 0.25 à 2 mg/mL	-2	2 médicaments	-2
VEMS de 40 % à 55 % pred	-3	CP 20 < 0.25 mg/mL	-3	3 médicaments	-3
VEMS < 40 % pred	-4			Stéroïdes oraux	-4

Évaluation: Le degré d'obstruction bronchique avant bronchodilatateur, au moment où le patient est stable, est la base à partir de laquelle la gravité de l'asthme et le déficit fonctionnel sont déterminés. L'échelle de déficit fonctionnel est fixée par le niveau d'hyperexcitabilité bronchique et la quantité de médicaments nécessaires.

Asthme	Obstruction bronchique	Hyperexcitabilité bronchique	Médicaments	Déficit fonctionnel
Aucun	0	0	0	0 %
Léger	0	1-2	0-2	5 % à 15 %
Modéré	1-2	1-3	1-3	20 % à 50 %
Grave	3-4	1-3	1-4	50 % à 100 %

*Méthode de DW Cockcroft et coll.: Clin Allergy 7:235, 1977.

VEMS: obstruction bronchique avant bronchodilatateur

CP 20: concentration d'histamine ou de méthacholine causant une chute de 20 % du VEMS

Après avoir confirmé objectivement l'asthme professionnel, la première étape consiste à retirer le patient du milieu de travail.

ne sont pas encore reconnues comme causes d'asthme professionnel, ou lorsque le monitoring de l'hyperexcitabilité bronchique est équivoque.

Les tests de provocation doivent être effectués en laboratoire par des médecins et un personnel expérimentés. Ces laboratoires doivent être accrédités par les autorités provinciales responsables de la pratique médicale dans la communauté.

Quand l'histoire suggère l'asthme professionnel, mais que le monitoring de l'asthme ne le confirme pas par des changements significatifs d'hyperexcitabilité bronchique, le travailleur doit être gardé sous observation. Si le diagnostic est confirmé lors des mois qui suivent, le travailleur pourra recevoir les conseils pertinents.

Tests démontrant la sensibilisation

Les tests cutanés et les tests *in vitro* de mesure d'anticorps de type IgE aux nombreuses causes d'asthme professionnel sont rarement disponibles. Plusieurs de ces tests n'ont été effectués que lors de recherche. Les travailleurs atteints d'asthme professionnel confirmé n'ont pas toujours une sensibilisation démontrable par des tests cutanés ou *in vitro*. Bien qu'un résultat de test positif témoigne de la sensibilisation à une substance, il est possible que le travailleur ne souffre pas

d'asthme si on l'expose à cette substance sur les lieux de travail. La nécessité pour les travailleurs sensibilisés et sans asthme d'éviter l'exposition éventuelle à l'agent responsable reste incertaine, mais ces personnes doivent être gardées sous surveillance.

Démarche

Après avoir confirmé objectivement l'asthme professionnel, la première étape consiste à retirer le patient du milieu de travail. Sans cela, l'asthme persistera, pourra augmenter et devenir permanent. Une fois que le travailleur est sensibilisé et atteint d'asthme, il est extrêmement improbable que des mesures préventives (telles la ventilation du milieu de travail ou l'utilisation de masques) préviendront des attaques ultérieures. Ainsi, des expositions inférieures à 0,001 partie par million peuvent être suffisantes pour provoquer de l'asthme chez certains employés sensibilisés aux isocyanates. Les employés sensibilisés qui ne changent pas de travail devraient être gardés sous surveillance médicale.

Que la cause soit professionnelle ou non, la médication anti-asthmatisque est la même. Les symptômes requièrent un traitement avec des médicaments sympathomimétiques et de la théophylline tel qu'indiqué. L'inflammation bronchique peut nécessiter un traitement aux

stéroïdes systémiques ou inhalés. Les autres médicaments peuvent être utilisés selon les indications. Le soulagement symptomatique peut masquer les effets de la sensibilisation et inciter le travailleur à continuer à travailler alors qu'il est encore atteint. Les travailleurs avec une hyperexcitabilité bronchique résiduelle devraient être informés des conséquences possibles de l'exposition aux substances irritantes.

Évaluation du déficit fonctionnel et de l'invalidité

Le déficit fonctionnel dans les maladies pulmonaires est évalué par le degré d'anomalie de la fonction pulmonaire qui est établi en fonction des anomalies de la mécanique pulmonaire et de la réponse respiratoire à l'exercice. Puisque la nature même de l'asthme comprend des inconstances, le degré de déficit fonctionnel changera dans le temps selon l'exposition à la cause ou le traitement. Dans l'asthme professionnel, la présence d'hyperexcitabilité bronchique est très utile pour évaluer le déficit fonctionnel (vu la nature variable de la maladie). L'hyperexcitabilité bronchique n'a pas été utilisée pour l'évaluation du déficit fonctionnel dans les maladies pulmonaires professionnelles. Cependant, son importance dans l'asthme professionnel devrait en faire un critère d'évaluation de cette maladie.

Lopid
gemfibrozil

Capsules à
300 mg

Agent antihyperlipidémique

MODE D'ACTION

Le LOPID abaisse les concentrations élevées de lipides dans le sérum en diminuant les triglycérides sériques avec réduction variable du cholestérol sérique total. L'effet inhibiteur se marque sur les fractions de lipoprotéines à faible densité (LDL) et très faible (VLDL). De plus, le LOPID peut augmenter la fraction de cholestérol des lipoprotéines à forte densité (HDL). Le mécanisme par lequel agit le LOPID n'est pas encore définitivement établi. Chez l'homme, il a été démontré que le LOPID provoquait l'inhibition de la lipolyse périphérique et la diminution de l'extraction hépatique des acides gras libres, réduisant ainsi la production de triglycérides hépatiques. Le LOPID inhibe également la synthèse des apoprotéines qui transportent les lipoprotéines à très faible densité (VLDL) résultant en une diminution des lipoprotéines à très faible densité (VLDL).

INDICATIONS

Le LOPID est indiqué comme adjuvant au régime alimentaire et aux autres mesures thérapeutiques dans le traitement des patients affectés d'hyperlipidémie de Type IV, et pour qui le risque de séquelles et de complications est très élevé. Le traitement initial de l'hyperlipidémie devrait inclure un régime spécifique, une réduction de poids et un programme d'exercices et, pour les patients diabétiques, un bon équilibre du diabète.

CONTRE-INDICATIONS

1. Dérèglement hépatique ou rénal, incluant la cirrhose biliaire primaire.
2. Maladie de la vésicule biliaire (voir mises en garde).
3. Hypersensibilité au gemfibrozil.
4. Ne pas administrer aux femmes enceintes ou aux mères qui allaitent.

MISES EN GARDE

1. Anticoagulants concomitants. Faire preuve de prudence en administrant des anticoagulants en même temps que le LOPID. Réduire la dose d'anticoagulant afin de maintenir le temps de prothrombine au niveau désiré afin d'éviter les complications hémorragiques.
2. Des études à long terme sur le gemfibrozil ont été réalisées sur les rats et les souris avec des doses une à dix fois supérieures à celles administrées à l'homme. La fréquence de nodules bénins et de cancers du foie a augmenté de manière significative chez les rats mâles soumis à de fortes doses. La fréquence de cancers du foie a également augmenté chez les rats mâles soumis à de faibles doses, mais cette augmentation n'était pas statistiquement significative ($P > 0,05$). Aucune différence statistiquement significative n'a été observée chez les sujets témoins en ce qui concerne la fréquence de tumeurs du foie des rates ou des souris mâles et femelles. Le nombre de tumeurs hépatiques et testiculaires a augmenté chez les rats mâles.
3. Calculs biliaires. Le LOPID peut augmenter l'excrétion de cholestérol dans la bile, résultant en la formation de calculs biliaires. Si des calculs biliaires sont soupçonnés, un examen de la vésicule biliaire est recommandé. Interrompre le traitement au LOPID en présence de calculs biliaires.
4. Puisque les effets du médicament sur la réduction de la mortalité due aux maladies coronaires n'ont pas été démontrés, n'administrer le LOPID qu'aux patients décrits dans la section "indications". Si une réduction significative des lipides dans le sérum n'est pas obtenue dans les 3 premiers mois, arrêter le traitement au LOPID.
5. Sa sécurité et son efficacité n'ont pas encore été établies dans le cas des enfants.
6. Les femmes fertiles ont à prendre des mesures anticonceptionnelles strictes. Si une grossesse survient malgré ces précautions, arrêter le traitement au LOPID.
7. Les femmes qui envisagent d'avoir un enfant devraient interrompre l'usage du LOPID plusieurs mois avant la conception.

PRÉCAUTIONS

1. Traitement initial. Avant d'établir le traitement au LOPID, essayer de maîtriser les lipides sériques par des mesures diététiques appropriées, des exercices, une perte de poids chez les patients obèses et le contrôle de l'équilibre du diabète sucré.
2. Traitement à long terme. Comme l'administration à long terme du LOPID est recommandée, effectuer des études chimiques avant de commencer le traitement, afin de s'assurer que le patient est effectivement atteint d'un taux élevé de lipides sériques ou d'un niveau bas de cholestérol de lipoprotéines à forte densité (HDL). Déterminer le niveau des lipides sériques à intervalles réguliers au cours du traitement au LOPID.
3. Affaiblissement de la fertilité. L'administration pendant 10 semaines à des rats mâles de doses de trois à dix fois supérieures aux doses normales pour l'homme, a résulté en une diminution de la fertilité. Des études ultérieures ont montré que ces effets s'inversaient après une période de 8 semaines de suspension du traitement et n'étaient pas transmis à leur progéniture.
4. Modifications de l'hémoglobine. Une faible réduction de l'hémoglobine ou de l'hématocrite a été observée occasionnellement chez des patients au stade initial du traitement au LOPID. Les niveaux se stabilisent par la suite durant le traitement à long terme. De ce fait, une numération globulaire est recommandée tous les deux mois durant la première année du traitement au LOPID.
5. Fonction hépatique. Des résultats anormaux de tests sur la fonction hépatique ont été observés occasionnellement au cours du traitement au LOPID; ce sont notamment des augmentations des transaminases (SGOT, SGPT), des phosphatases alcalines et de LDH. Ces phénomènes sont généralement réversibles à l'arrêt du traitement au LOPID. De ce fait, des examens périodiques du système hépatique sont recommandés et le traitement au LOPID devrait être interrompu si les anomalies persistent.
6. Administrer le LOPID avec prudence chez les patients ayant des antécédents d'ictère ou de maladie hépatique.
7. Arythmie cardiaque. Bien qu'aucune anomalie clinique significative, qui puisse être attribuée au LOPID, n'ait été rapportée, cette possibilité pourrait tout de même exister.

EFFETS SECONDAIRES

Le gemfibrozil a été soigneusement mis à l'épreuve sur plus de 3 000 patients au cours d'études contrôlées en clinique. Les symptômes rapportés pendant la phase de contrôle de l'étude de 805 sujets, ont été évalués selon leur gravité. Les symptômes qui figurent sur la liste se sont présentés chez au moins cinq patients; toutes les réactions cutanées ont été rapportées quelle que soit leur fréquence. Les principaux symptômes, dont la fréquence a été plus forte avec gemfibrozil par rapport à celle de placebo, touchent l'appareil digestif. La nausée et le vomissement, les douleurs abdominales et épigastriques sont apparus plus fréquemment dans le groupe gemfibrozil que dans le groupe placebo. Toutefois, la fréquence était très faible: la nausée, 4,3% avec gemfibrozil par rapport à 3,8% avec placebo; le vomissement, 2,3% par rapport à 0,8%; les douleurs abdominales, 6,4% par rapport à 4,2% et la douleur épigastrique, 3,4% par rapport à 1,7%.

SYMPTÔMES ET TRAITEMENT DU SURDOSAGE

Aucun cas de surdosage n'a été rapporté; si le cas se présentait, des mesures de soutien devraient être prises en fonction des symptômes.

POSOLOGIE

La dose recommandée pour les adultes est de 1 200 mg et doit être administrée en deux doses fractionnées, une demi-heure avant les repas du matin et du soir. La dose maximale recommandée est de 1 500 mg.

PRÉSENTATION

La couleur des capsules de LOPID est blanche et marron. Chaque capsule contient 300 mg de gemfibrozil. Flacons de 100.

Monographie du produit disponible sur demande.

Le travailleur devrait être évalué rapidement après le retrait de l'exposition à l'agent causal et à des intervalles de deux ans pour déterminer les effets chroniques.

L'invalidité est déterminée par le degré d'atteinte fonctionnelle et les exigences du travail. Les besoins énergétiques requis pour l'exécution de la tâche doivent être considérés dans l'établissement du degré d'invalidité. Tout déficit fonctionnel dans les pneumoconioses est constant et il existe une relation entre les tests à l'exercice et ce déficit fonctionnel.

L'asthme professionnel a des traits uniques: premièrement, la spécificité de la cause de l'asthme; deuxièmement, la variabilité des symptômes asthmatiques et, troisièmement, l'hyperexcitabilité des bronches à des stimuli non spécifiques. Une fois sensibilisé, un travailleur asthmatique soumis à une exposition continue peut développer un asthme qui continue après l'exposition à l'agent causal. Le travailleur devient alors incapable d'effectuer le travail qui a causé son asthme. Il est préférable de reconnaître l'incapacité du travailleur à accomplir ses tâches le plus rapidement possible. Une fois que l'exposition à l'agent causal a cessé, le degré du déficit fonctionnel relié à l'invalidité peut être évalué. Pour déterminer cette invalidité, il est essentiel que l'évaluation du

PARKE-DAVIS

Parke-Davis Canada Inc., Scarborough, Ontario

PAAB
CCPP

M. dép. de Parke, Davis & Company, Parke-Davis Canada Inc., usager aut.

ACIM

déficit fonctionnel comprenne une mesure de l'hyperexcitabilité bronchique et la médication nécessaire à l'amélioration de la condition asthmatique. Puisque l'asthme est variable, des évaluations répétées seront nécessaires.

Le tableau 2 présente une méthode d'évaluation du déficit fonctionnel et de l'invalidité. Ce schéma est basé sur celui qui est utilisé par la Commission de santé et de sécurité du travail du Québec. Il est cependant moins détaillé et présente uniquement les principes de base de l'évaluation du déficit fonctionnel.

Le diagnostic précoce de l'asthme professionnel et la cessation rapide de l'exposition à l'agent causal facilitent la disparition ou le contrôle de l'asthme, permettant ainsi au travailleur de reprendre rapidement un autre travail. Cependant, le déficit fonctionnel résiduel et l'invalidité peuvent se produire plus fréquemment et à des intervalles plus longs que prévus. Le travailleur doit être évalué à nouveau à des intervalles de deux ans pour permettre d'établir l'invalidité permanente.

Handicaps

Les conséquences financières et sociales de l'asthme professionnel doivent être réduites au minimum. Le travailleur a droit à une consultation auprès d'un médecin apte à poser un diagnostic précis et à éva-

luer la nécessité d'un changement de travail. Le travailleur doit recevoir l'assurance qu'une compensation financière lui sera versée et que les comités de compensation vont amorcer les démarches nécessaires pour lui trouver un nouvel emploi. Quand ils évaluent de tels cas, les comités de compensation doivent compter sur les services d'un médecin qui connaît l'asthme professionnel. Ces comités doivent travailler rapidement afin que les travailleurs puissent décider plus facilement s'ils doivent changer de travail pour améliorer leur condition asthmatique et éviter des délais inutiles.

Prévention

Les autorités provinciales et fédérales responsables de la santé et de la sécurité des travailleurs doivent identifier les industries utilisant des agents qui causent l'asthme et aviser les personnes concernées des risques qu'encourent leurs employés. Les industries qui exposent des travailleurs à des causes confirmées d'asthme professionnel doivent s'assurer que les concentrations de ces substances sont réduites et que tous les efforts sont faits pour prévenir des déversements qui pourraient déclencher la sensibilisation.

Bien qu'il faille aviser les travailleurs qu'ils courent des risques de développer l'asthme et qu'ils

peuvent obtenir de l'aide médicale, rien ne prouve qu'un programme médical de dépistage périodique soit utile. Le dépistage avant l'embauche est une mesure tentante puisqu'elle permet d'identifier les travailleurs susceptibles de développer l'asthme professionnel. Il y a peu de preuve que les sujets qui souffrent déjà d'asthme soient à plus grand risque de développer de l'asthme professionnel. Cependant, puisque le diagnostic d'asthme professionnel peut être compliqué par l'existence antérieure de la maladie, ces sujets ne devraient probablement pas être mis en contact avec un agent causal connu.

Bien que les travailleurs atopiques aient un plus grand risque de sensibilisation à des agents de hauts poids moléculaires que les sujets non atopiques, le risque n'est pas suffisant pour justifier le dépistage et l'élimination avant l'embauche. Le recours à des mesures d'hyperexcitabilité bronchique avant l'embauche pour déterminer la capacité d'effectuer un emploi n'est pas justifié.

Les figures contenues dans cet article ont été ajoutées par le docteur Malo et n'engagent pas la responsabilité de la Société de thoracologie du Canada.

Nous tenons à remercier Colette Quesnel d'avoir relu la traduction de ce document.

Screening For Occupational Asthma: A Word of Caution

Gail M. McNutt, MD; Donald P. Schlueter, MD; and Jordan N. Fink, MD

The diagnosis of occupational asthma may be difficult due to the complex mechanisms inducing the disorder. Identification of the offending agent after historical documentation may be difficult without bronchial challenge. The hallmark of asthma is bronchial hyperreactivity as detected by methacholine challenge, and this test could be considered as a screening test for asthma in the workplace. Four cases are presented that document changes in methacholine airway reactivity dependent on temporal association with exposure to the workplace or to the specific offending agent. This indicates a need for a careful evaluation of symptoms relative to exposure in patients suspected of workplace asthma as well as serial determinations of methacholine response to detect potential variability in the airway reactivity.

The most frequently diagnosed occupationally related diseases involve the respiratory system because it is a portal of entry for irritant, sensitizing, or toxic agents in the work environment.¹ A variety of chemicals and organic dusts encountered in the workplace can induce pulmonary responses,^{2,3} but fortunately the number of individuals affected is usually small. Although both asthma and hypersensitivity pneumonitis have been associated with these exposures, occupational asthma appears to be the most prevalent disorder.⁴ The recognition of occupational asthma can be difficult because of the large number of potential offending agents, the extremely diverse range of materials and processes that are involved in the workplace, and the variability in the

temporal relationship of the pulmonary response and the workers exposure.⁵

The diagnosis of occupational asthma is frequently complex, requiring evidence of sensitization to the suspected causative agent, as well as evidence that the agent can provoke the clinical manifestations of the disease. Sensitization by immunoglobulin E-mast cell mediator release mechanisms may be demonstrated in vivo by using skin tests or in vitro with radioallergosorbent or enzyme-linked immunoassays or antigen-stimulated histamine release from basophils. Confirmation of a causal relationship between the workplace and occupational asthma has been based on inhalation challenge, either by removal from and return to the work environment, or, where a specific agent has been identified, controlled challenge in the laboratory.⁶⁻⁷ Reproduction of the clinical symptoms and physiologic changes thus identifies the sensitized individual. This type of testing can be uncomfortable for the patient, at times insensitive⁸ and expensive. Therefore, it is advantageous to have some type of preliminary screening test for evaluating a patient suspected of having occupational asthma.

The hallmark of asthma regardless of etiology is bronchial hyperreactivity. The hyperreactivity can usually be demonstrated in individuals with occupational asthma by using methacholine inhalation challenge. However, a number of factors may influence the results of this testing and thus obscure its interpretation. Studies of nonspecific airway hyperreactivity in response to methacholine have demonstrated variability with stimuli such as inhaled aeroallergen,⁹ respiratory infection,¹⁰ ozone,¹¹ chemicals,¹² and immunizations.¹³ Recognition of the variability in nonspecific airway hyperreactivity can be important in the diagnosis of and screening for occupational asthma. The following cases (summarized in the Table) illustrate the need for careful temporal evaluation of some patients with suspected occupational asthma, as the associated airway hyperreactivity may vary in relation to exposure to the inciting agent.

From the Department of Medicine, Medical College of Wisconsin, Milwaukee, Wis (Dr McNutt, Fellow, Allergy-Immunology Division; Dr Schlueter, Professor of Medicine, Pulmonary and Critical Care Division; Dr Fink, Professor of Medicine, Chief, Allergy-Immunology Division).

Address correspondence to Jordan N. Fink, MD, 8700 W Wisconsin Ave, Milwaukee, WI 53226.

0096-1736/91/3301-0018\$03.00/0

Copyright © by American College of Occupational Medicine

Table
Characteristics of Patients Evaluated

Patient	Age/Sex	Symptoms	Work Exposure	Methacholine Reactivity*	Work Status
1	40/F	Cough, chest tightness	Epoxy resin	4/25/88 - 5/26/88 +	off work for 2 days working
2	39/F	Angioedema, urticaria, dyspnea	Candy manufacturer (peanut, rice, chocolate)	4/17/87 + 6/08/87 - 6/23/87 + 7/30/87 -	working off work working off work
3	27/F	Cough, dyspnea, chest tightness	Toluene diisocyanate	3/23/88 - 4/01/88 +† 4/11/88 +‡	working working working
4	32/M	Cough, wheeze, chest tightness	Ducks	4/13/89 - 8/30/89 +§	working working

* Decrease in FEV₁ of 20% or more after inhalation challenge.

† Associated with a toluene inhalation challenge.

‡ After toluene diisocyanate inhalation challenge.

§ After *Aspergillus fumigatus* inhalation challenge.

Methods

All patients were seen in the Allergy-Immunology Clinic of the Medical College of Wisconsin Affiliated Hospitals. Skin testing was carried out by using prick or intracutaneous techniques with commercial antigens or antigens cultured and prepared from the patient's environment. Cultures of appropriate environments were carried out on Sabouraud's media and antigens were prepared from the cultures on a 10% weight by volume basis.

Inhalation challenges were done with methacholine or antigen in the pulmonary function laboratory using standard techniques.¹⁴ All patients were observed and monitored for up to 12 hours.

Toluene diisocyanate challenge concentration was monitored with a MDA Series 7100 Toxic Gas Monitor (MDA Scientific, Inc, Lincolnshire, Ill). *Aspergillus* cultured from the workplace environments was not used for inhalation challenge because of known contamination of the organism with aflatoxin, a potential carcinogen. Instead, commercially available *Aspergillus fumigatus* extracts (Greer Laboratories, Lenior, NC) was used at a 10% weight by volume concentration.

Case Reports

Case 1

A 40-year-old woman had been employed for 11 years assembling gas appliance parts that involved the use of epoxy resins. She presented with a 6-year history of cough and chest tightness occurring while at work. Her symptoms resolved on weekends and holidays when away from the work environment.

Pulmonary function studies performed April 25, 1988 after 2 days away from work demonstrated normal spirometry and a negative methacholine challenge (10% decrease in forced expiratory volume in 1 second (FEV₁) at a concentration of 25 mg/ml).

These studies were repeated on May 26, 1988 after she had worked for 4 hours. At that time spirometry remained normal but the methacholine challenge was now positive (23% decrease in FEV₁ at a concentration of 2.5 mg/ml). She subsequently resigned her job and with avoidance of exposure has remained asymptomatic.

Case 2

A 39-year-old woman had been employed for 1 year in a candy manufacturing plant where she was exposed to peanuts, rice, chocolate, and packaging materials. She described recurrent urticaria, angioedema, and mild dyspnea over a 7-month period. Her symptoms worsened at the end of her work shift and resolved on weekends away from work. Evaluation of the work environment revealed *Aspergillus niger* colonizing the ventilation system. Immediate wheal and flare skin reactivity could be demonstrated to an extract of the cultured *Aspergillus*.

Methacholine challenges were performed on four occasions: two while she was working and two while she was on medical leave of absence. While working, both challenges were positive (a 23% decrease in FEV₁ at a concentration of 5 mg/ml and a 28% decrease in FEV₁ at a concentration 12.5 mg/ml). While on medical leave from work, both challenges were negative (a 7% decrease in FEV₁ at a concentration of 25 mg/ml and a 14% decrease in FEV₁ at a concentration of 25 mg/ml). She changed employment, noted prompt resolution of her symptoms, and has had no recurrences.

Case 3

A 27-year-old woman had been employed in the production of polyurethane foam car seats with exposure to toluene diisocyanate (TDI) for 10 months. She had early morning waking with cough, dyspnea, and chest tightness for the previous 7 months.

No immediate wheal and flare skin reactivity could be detected with TDI and diphenylmethane diisocyanate conjugates to human serum albumin (supplied by C. R. Zeiss, MD, American Academy of Allergy and Immunology Occupational Asthma Committee).

Pulmonary function testing on March 23, 1988 demonstrated normal spirometry and negative methacholine challenge (a 17% decrease in FEV₁ at a concentration of 25 mg/ml). On April 1, 1988 she was exposed, as a control, to the vapor of a 1:100 solution of toluene for 30 minutes. A methacholine challenge immediately afterward was markedly positive (a 68% decrease in FEV₁ at a concentration of 25 mg/ml). This strongly suggests a component of respiratory tract irritation. It is noteworthy that she had no late phase response after this exposure. Ordinarily a control inhalation challenge is performed with saline or an antigen to which, by history and skin testing, the individual is not sensitized. Toluene, although it is a respiratory irritant, is not known to cause late phase hypersensitivity reactions. A positive methacholine test must be interpreted with caution when the occupational environment contains respiratory irritants in addition to the suspected antigen.

On April 11, 1988 she was exposed to TDI vapor at a mean concentration of 3.5 ppb for 15 minutes (American Conference of Governmental and Industrial Hygienists recommendation 8 hour time-weighted average of 5 ppb with excursions to a ceiling of 20 ppb for four 15-minute periods a day). Preexposure pulmonary function was normal and unchanged from the initial testing. After TDI challenge, the maximal decline in pulmonary function occurred at 6 hours postexposure with a decrease of 23% in forced vital capacity, 28% in FEV₁, 40% in forced expiratory flow, mid-expiratory phase, and 13% in diffusing capacity. A methacholine challenge at 7.5 hours after TDI vapor exposure was positive with a 20% decrease in FEV₁ at a concentration of 12.5 mg/ml. In contrast to the immediate irritant effect of toluene, the late phase response to TDI challenge is much more suggestive of true immunologic sensitivity. She is no longer involved in auto seat manufacturing but continues to have mild asthma.

Case 4

A 32-year-old man had been employed for 6 years on a duck farm, and was involved with care and processing of up to 35,000 ducks per day. He presented with a 4-year history of asthma, which was poorly controlled despite the use of an inhaled beta agonist and cromolyn. He began to wheeze several hours after leaving work, but had no symptoms at work. He was well on weekends or while on vacation.

A culture of duck droppings grew *Aspergillus flavus*. Immediate wheal and flare reactivity could be detected to duck serum and *A fumigatus*, but not to the cultured *A flavus*.

Pulmonary function testing on April 13, 1989 revealed normal spirometry and a negative methacholine challenge (a 5% decrease in FEV₁ at a concentration of 25

mg/ml). A bronchial challenge with duck serum was negative.

As previously noted, the cultured *A flavus* was not used for bronchial challenge because of known contamination of the organism with aflatoxin, a carcinogen. Instead, bronchial provocation with the related antigen *A fumigatus* was performed on August 30, 1989. There was no significant change in pulmonary function after the challenge, but a methacholine challenge 9 hours afterward was positive with a 39% decrease in FEV₁ at a concentration of 25 mg/ml. He now uses a particle respirator and inhaled cromolyn while working and is symptom-free.

Discussion

These cases illustrate the variability of methacholine responsiveness in relationship to antigen exposure in some workers with occupational asthma. This variability, therefore, mandates a need for a careful temporal evaluation of symptoms relative to exposure in patients suspected of workplace asthma.

The first two cases presented illustrate variability in the methacholine reactivity temporally related to workplace exposure. The last two cases demonstrate the development of nonspecific airways hyperreactivity after exposure to specific antigen through bronchial provocation challenge and, in case 3, to a nonspecific bronchial irritant. In the duck farm worker, airway hyperreactivity was induced after inhalation of a related antigen. The lack of response to antigen during the challenge of this worker in the face of workplace symptoms when exposed may be related to the dose of antigen used for inhalation challenge or the need for intercurrent exposure to other workplace agents. Furthermore, inasmuch as only a single batch of duck droppings was cultured, other sensitizing organisms may have been present in the workplace. The initial negative methacholine challenge in these two cases, despite workplace exposure, may have been the result of variable antigen exposure the day of testing or a temporal delay in symptom onset after exposure.

Variable nonspecific airways hyperreactivity is associated with inflammation, epithelial edema, and mediator release. An increased number of basophils and mast cells in the bronchoalveolar lavage of asthmatic patients supports underlying inflammation.¹⁵ In controlled asthma, increased methacholine responsiveness has been demonstrated to occur in the absence of increased epithelial permeability or a decrease in airway caliber.^{16,17} Barnes¹⁸ has proposed that airway epithelial damage may result in the stimulation of C-fiber afferent nerves with resultant release of sensory neuropeptides such as substance P. Such neuropeptides can cause airway smooth muscle contraction, mucous hypersecretion, and airway edema. This may well be an underlying mechanism in increased airway reactivity, with initial antigen exposure leading to epithelial damage through mediator release from sensitized cells.

Given the variability of exposure and symptom onset,

the advantages of intrashift serial pulmonary function studies are apparent. Although spirometry and methacholine challenge are not easily available on this basis, the peak flow meter has been used to provide serial measurement in the workplace.¹⁴ The peak flow measurement is highly effort dependent and may not be reliable in patients seeking compensation.

Although the demonstration of bronchial hyperreactivity by methacholine challenge is not diagnostic of occupational asthma or its etiologic agent, it is a useful adjunct in documenting the clinical manifestation of disease and temporal relationships to the workplace environment. Awareness of the variability with exposure to the workplace as illustrated by our patients will assist in accurate interpretation of test results. We would, therefore, advocate careful and repeated pulmonary function testing, to include methacholine challenge. Such serial testing will likely uncover or clarify patients with suspected but not clearly proven occupational asthma.

Acknowledgments

The authors thank Barbara Miller for her technical assistance and Mary Ann Braasch for editorial assistance.

References

1. Cullen MR, Cherniack MG, Rosenstock L. Medical progress: occupational medicine. *N Engl J Med*. 1990;322:594-601.
2. Chan-Yeung M, Lam S. State of Art: occupational asthma. *Am Rev Respir Dis*. 1986;133:686-703.
3. Salvaggio JE. Hypersensitivity pneumonitis. *J Allergy Clin Immunol*. 1987;79:558-571.
4. Venables KM. Epidemiology and the prevention of occupational asthma. *Br J Ind Med*. 1987;44:73-75.
5. Schlueter DP. Environmental challenge. *Allergy Proc*. 1989;10:339-344.
6. Pepys J, Hutchcroft BJ. Bronchial provocation tests in etiologic diagnosis and analysis of asthma. *Am Rev Respir Dis*. 1975;112:829-859.
7. Hendrick DJ. Bronchopulmonary disease in the workplace: challenge testing with occupational agents. *Ann Allergy*. 1983;51:179-184.
8. Moller DR, Brooks SM, McKay RT, Cassidy K, Koss S, Bernstein IL. Chronic asthma due to toluene diisocyanate. *Chest*. 1986;90:494-499.
9. Boulet LP, Cartier A, Thomson NC, Roberts RS, Dolovich J, Hargreave FE. Asthma and increases in nonallergic bronchial responsiveness from seasonal pollen exposure. *J Allergy Clin Immunol*. 1983;71:399-406.
10. Empey DW, Laitinen LA, Jacobs L, Gold WM, Nadel JA. Mechanisms of hyperreactivity in normal subjects after upper respiratory tract infection. *Am Rev Respir Dis*. 1976;113:131-139.
11. Golden JA, Nadel JA, Boushey HA. Bronchial hyperirritability in healthy subjects after exposure to ozone. *Am Rev Respir Dis*. 1978;118:287-294.
12. Fabbri LM, Boschetto P, Zocca E, Gianfranco M, Fausto P, Mario P, et al. Bronchoalveolar neutrophilia during late asthmatic reactions induced by toluene diisocyanate. *Am Rev Respir Dis*. 1987;136:36-41.
13. Ouellette JJ, Reed CE. Increased response of asthmatic subjects to methacholine after influenza vaccine. *J Allergy*. 1965;36:558-563.
14. Naclerio RM, Norman PS, Fish JE. In vivo method for study of allergy: mucosal tests, techniques and interpretation. In: Middleton E, Reed CE, Ellis EF, Adkinson NF, Yunginger JW, eds. *Allergy, Principles and Practices*. 3rd ed., St Louis, MO: C. V. Mosby; 1988:437.
15. Flint KC, Leung KBP, Hudspeth BN, Brostoff J, Pearce FL, Johnson NM. Bronchoalveolar lavage mast cells in extrinsic asthma: a mechanism for the initiation of antigen specific bronchoconstriction. *Br Med J*. 1985;291:923.
16. Hogg JC. Bronchial mucosal permeability and its relationship to hyperreactivity. *J Allergy Clin Immunol*. 1981;67:421-425.
17. Cartier A, Thomson NC, Frith PA, Roberts R, Hargreave FE. Allergen induced increase in bronchial responsiveness to histamine: relationship to the late asthmatic response and change in airway caliber. *J Allergy Clin Immunol*. 1982;70:170-177.
18. Barnes PJ. Asthma as an axon reflex. *Lancet*. 1986;1:242-244.

Respiratory symptoms, lung function, and sensitisation to flour in a British bakery

A W MUSK,¹* K M VENABLES,¹ B CROOK,²† A J NUNN,³ R HAWKINS,¹ G D W CROOK,¹ B J GRANEK,¹ R D TEE,¹ N FARRER,¹ D A JOHNSON,³ D J GORDON,¹ J H DARBYSHIRE,¹ A J NEWMAN TAYLOR¹

From the Department of Occupational Medicine,¹ National Heart and Lung Institute, Brompton Hospital, London SW3 6HP, AFRC Institute of Arable Crops Research,² Rothamsted Experimental Station, Harpenden, Herts, and MRC Cardiothoracic Epidemiology Group,³ Brompton Hospital, London SW3 6HP, UK

ABSTRACT A survey of dust exposure, respiratory symptoms, lung function, and response to skin prick tests was conducted in a modern British bakery. Of the 318 bakery employees, 279 (88%) took part. Jobs were ranked from 0 to 10 by perceived dustiness and this ranking correlated well with total dust concentration measured in 79 personal dust samples. Nine samples had concentrations greater than 10 mg/m³, the exposure limit for nuisance dust. All participants completed a self administered questionnaire on symptoms and their relation to work. FEV₁ and FVC were measured by a dry wedge spirometer and bronchial reactivity to methacholine was estimated. Skin prick tests were performed with three common allergens and with 11 allergens likely to be found in bakery dust, including mites and moulds. Of the participants in the main exposure group, 35% reported chest symptoms which in 13% were work related. The corresponding figures for nasal symptoms were 38% and 19%. Symptoms, lung function, bronchial reactivity, and response to skin prick tests were related to current or past exposure to dust using logistic or linear regression analysis as appropriate. Exposure rank was significantly associated with most of the response variables studied. The study shows that respiratory symptoms and sensitisation are common, even in a modern bakery.

Occupational asthma and rhinitis occur in bakers¹ and the environmental agents responsible appear to be components of the grain itself²⁻⁴ or grain contaminants, such as mites, weevils, and moulds.⁵⁻⁷ The relative importance of these potential allergens may vary according to the source of the flour, conditions of storage, and intensity of exposure. Recent papers describing grain components as important allergens have come from Australia,^{3,4} where grain has a low moisture content. A higher moisture content, or storage of grain or flour for long periods, may promote the growth of contaminant micro-organisms, mites, and insects. Materials added to flour before baking, such as yeast and amylase, derived from *Aspergillus* species,⁸ may also be allergenic.

As many as a third of bakers and grain workers may show evidence of sensitisation,⁹⁻¹¹ which appears to be related to intensity and duration of exposure in the industry as well as to host factors, such as atopy.^{11,12} Mechanisms involving IgE and the mast cell have been implicated,^{12,13} but precipitins to components of flour have also been identified³ and non-immunological processes, such as direct activation of complement pathways, may be involved.¹⁴

Apart from case reports, there is little information about asthma and sensitisation in British bakers. This study was designed to (a) describe the levels of exposure to bakery dust in a modern British bakery, (b) estimate the prevalence of symptoms and sensitisation in the workforce of the bakery, and (c) explore relations between indices of exposure and response.

Methods

STUDY DESIGN AND SUBJECTS

The study was a cross sectional survey of current employees conducted over six consecutive days and nights. All current workers with the exception of

*Present address: Sir Charles Gairdner Hospital, Nedlands, Western Australia.

†Present address: Occupational Medicine and Hygiene Laboratories Health and Safety Executive, London NW2 6LN.

Accepted 24 October 1988

Respiratory sy
drivers and sa
involved only 1
invited to part

DETERMINATI
CONCENTRAT
Concentration
zones of work
samplers. Eith
London) hous
microfibre fil
nominal pore
diameter three
(Millipore, Ha
size polycarb
Sterilin; Houn
to portable, bi
123, Casella or
bury) sampling
The bakery
separate areas:
ery bakery fo
pastries, the ho
and crumpets;
tion offices and
employees wor
eight hours to
total airborne d

EXPOSURE RA
Independently
tions, each em
scale of 0 to 10
manager in
physician from

Table 1 Number

Rank	Employment
0	Office, transport, staff
1	Despatch, staff
2	Slicers, wrapping
3	Bakery machine
4	Production
5	Bakery machine
6	Staff attendants
7	Bakery cleaners
8	bread baking
9	Doughnut (hot plant)
10	Staff preparing bakery
	Flour room
	Total

Percentages in rows
10 mg/m³ (the expo

drivers and salesmen, whose contact with the bakery involved only the collection of goods for delivery, were invited to participate in the study.

DETERMINATION OF CURRENT EXPOSURE CONCENTRATIONS

Concentrations of airborne dust in the breathing zones of workers were determined with personal air samplers. Either open faced filter holders (Casella, London) housing preweighed 25 mm diameter glass microfibre filters (GF/A, Whatman, Maidstone; nominal pore size 1.6 μm), or closed face 37 mm diameter three piece polystyrene aerosol monitors (Millipore, Harrow) housing preweighed 0.8 μm pore size polycarbonate membrane filters (Nuclepore; Sterilin; Hounslow) were used. These were connected to portable, battery operated vacuum pumps (AFC-123, Casella or L2SF, Rotheroe and Mitchell, Aylesbury) sampling at air flow rates of 2 l/min.

The bakery was divided into five main structurally separate areas: the main bread bakery; the confectionery bakery for producing buns, rolls, scones, and pastries; the hot plate bakery for producing pancakes and crumpets; the workshop area; and the administration offices and canteen. Within each area one or more employees wore sampling devices for periods of up to eight hours to provide gravimetric measurements of total airborne dust.

EXPOSURE RANKING

Independently of the measurement of dust concentrations, each employment category was ranked on a scale of 0 to 10 for perceived dustiness by the bakery manager in consultation with an occupational physician from the baking industry (table 1). Office,

transport, and workshop staff who worked in physically separate accommodation and never entered production areas were graded 0, whereas subjects working in the flour room or in the manufacture of scones were graded 10.

WORKPLACE EXPOSURE MEASUREMENTS

Seventy nine personal dust samples were collected throughout the bakery (table 1). Nine of the samples had concentrations in excess of the exposure limit for nuisance dust (10 mg/m^3).¹³ The geometric mean total dust concentrations were, in general, consistent with the rank of workplace exposure (table 1) but there was considerable variation within some exposure ranks, such as exposure rank 6.

RESPIRATORY QUESTIONNAIRE

All participants completed a self administered questionnaire on respiratory symptoms based on the Medical Research Council (MRC) Questionnaire (1976). Additional questions were added to indicate whether the respiratory symptoms experienced (breathlessness, wheeze, chest tightness, and sneezing or itchy, running nose) improved on days off work or on holidays (if they did they were considered to be work related). Further questions asked if the participant thought that work "affected" his or her chest, or nose. Participants also completed questions on smoking habits and on occupational history. Smokers were defined as those who had smoked at least one cigarette a day or equivalent in other tobacco products for at least one year and ex-smokers had ceased smoking at least six months before the study.

Chronic bronchitis was defined as sputum production on most days for at least three months each year.

Table 1 Number of employees participating in the study and results of dust sampling by exposure rank

Rank	Employment	Total No of employees	Participants		No of samples tested	Dust sampling total dust (mg/m^3)	
			No	%		Range	Geometric mean
0	Office, transport, and vehicle-workshop staff	52	37	71	1	0.18	0.18
1	Despatch, traywashing, nursing, and canteen staff	23	23	(100)	2	0.00-0.08	0.01
2	Slicers, wrappers, and packers	84	70	83	23	0.00-3.65	0.34
3	Bakery manager, quality control staff	7	6	(86)	0	—	—
4	Production foremen, security staff	29	28	97	5	0.01-0.99	0.24
5	Bakery maintenance staff	20	19	(95)	1	2.97	2.97
6	Staff attending ovens or in cooking areas	29	26	90	16 [3]	0.00-37.57	1.73
7	Bakery cleaning staff, doughmakers (main bread bakery)	57	54	95	12 [2]	0.01-16.80	2.13
8	Doughmakers (confectionery bakery), mixers (hot plate bakery)	9	9	—	10 [1]	0.59-14.10	2.69
9	Staff preparing ingredients in confectionery bakery	2	2	(94)	2 [1]	9.97-12.05	11.00
10	Flour room staff, scone production staff	6	5	—	7 [2]	1.84-13.03	6.59
	Total	318	279	88	79 [9]	—	—

Percentages in round parentheses are based on fewer than 25 subjects. Numbers in square parentheses refer to samples with levels above 10 mg/m^3 (the exposure limit for nuisance dust is 10 mg/m^3).

Dyspnoea was defined as being troubled by shortness of breath when hurrying on level ground or walking up a slight hill.

PULMONARY FUNCTION

Forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) were measured with one of four dry wedge spirometers (Vitalograph, Buckingham). These were checked for leakages and calibration (using a one litre syringe) at least three times each day. Measurements were expressed at ATPS and a calibration factor for each spirometer was included. The best FEV₁ and the best FVC was taken from three technically satisfactory forced expiratory manoeuvres where the best two recordings were within 5% of each other.* All measurements were made at an ambient temperature within the range 18–23°C.

Each individual's FEV₁ and FVC was divided by the square of height and standardised to age 25 years using age regression coefficients calculated from the study participants. Separate linear regressions were used for subjects over or under 25.

NON-SPECIFIC BRONCHIAL REACTIVITY

Non-specific bronchial reactivity was measured by the method of Yan *et al*¹⁷ using hand held De Vilbiss No 40 nebulisers to a total cumulative dose of methacholine of 120 mcumol. The provocative cumulative dose of methacholine producing a 20% fall relative to the postsaline FEV₁ (PD₂₀) was calculated by linear interpolation of the final two points on a logarithmic scale.

SKIN PRICK TESTS

Skin prick tests were performed on the flexor surface of the forearm using the following allergen extracts: B2 grass pollen (4100, Bencard), *Dermatophagoides pteronyssinus* (2801, Bencard), cat fur (3204, Bencard), wheat grain (5101, Bencard), *Aspergillus fumigatus* (2000, Bencard) bakers yeast (7902, Bencard), mould mix (*Alternaria alternata*, *A. fumigatus*, *Cladosporium herbarum*, *Penicillium notatum*, Dome/Hollister Stier), *Tribolium confusum* (5 mg/ml, Health and Safety Executive, London), mixed flour (5105, Bencard), *Tyrophagus longior* (5 mg/ml, Health and Safety Executive, London), *Acorus sira* (5 mg/ml, Health and Safety Executive, London), *Glycyphagus destructor* (5 mg/ml, Health and Safety Executive, London), *Tyrophagus putrescentiae* (5 mg/ml, 78/517 National Institute of Biological Standards and Control), and *G. domesticus* (5 mg/ml, Brompton Hospital). Positive control was histamine dihydrogen chloride and negative control was Coca's solution. All tests were read at 10 minutes. The mean of the greatest dimension of the weal and the dimension at right angles to this was calculated. A mean weal diameter of 2 mm or

more greater than the negative control was considered positive. Subjects were classified as atopic if they had one of more positive responses to common allergens (grass pollen, *D. pteronyssinus*, or cat fur). They were considered "grain mite positive" if they had a positive response to *T. longior*, *A. sira*, *G. destructor*, *T. putrescentiae*, or *G. domesticus*. Additionally, if *T. confusum*, baker's yeast, mixed flour, wheat grain, mould mix, *A. fumigatus*, or any of the grain mites were positive subjects were classified as "bakery antigen positive."

STATISTICAL PROCEDURES

The statistical significance of the relation of potential explanatory variables to symptoms, bronchial reactivity, and skin response was examined by using logistic regression analysis; the relation to FEV₁/FVC ratio was analysed using linear regression.¹⁸ The independent explanatory variables included in the analyses were age, sex, current smoker, ever smoked, atopic status, years worked in the bakery, current exposure rank, whether currently working at exposure rank 6 or more, and whether ever worked at exposure rank 6 or more.

Results

CHARACTERISTICS OF THE SUBJECTS

A total of 279 (88%) of the 318 bakery employees took part in the survey (table 1), 92% of the men and 82% of the women. Two men and three women were unavailable because of illness and two men and one woman were on holiday. Twelve men and 19 women refused to take part in the study. Of the 39 workers who did not take part, 15 were from rank 0 (with the lowest exposure), six from rank 2, and one from rank 3. In all other exposure categories at least 90% of work force took part.

Twenty six male workers (a subset of exposure rank 7) were employed only on Saturdays to clean the bakery during its non-production day. They were much younger than the other workers (all were 20 or under compared with the remainder of the male work force of whom 77% were 25 or more) and all but two had been employed for less than two years. In addition 19 male maintenance workers (all those in exposure rank 5) had intermittent exposure. These two groups were therefore considered separately from the main group and are referred to as the intermittent exposure group in all subsequent analyses. The multivariate analyses identified a history of exposure rank 6 or more (past or present) to be the measure of exposure most frequently associated with response variables. Therefore the results in tables 2–4 are presented according to this categorisation of exposure.

In all, 55% of the workers in the main group were men (table 2) but the proportion varied in the different exposure categories. About half the workers had been

Respiratory sy

Table 2 Chara rank. (Percentage subjects)

Sex: Male
Age (yr): <25
25–44
≥45
Years employed in:
<2
2–10
>10
Smoking status:
Current smoker
Ex-smoker
Never smoked
Atopic:
Total assessed

*A subset of exposure rank 6 or more.

Table 3 Sympt. (Percentages in subjects)

Symptoms
Chronic bronchitis
Dyspnoea
Wheeze:
Any
Work related
Chest tightness:
Any
Work related
Difficulty in breath
Any
Work related
Any chest symptom
Any
Work related
Nasal symptoms:
Any
Work related
Any chest or nasal
Any
Work related
"Work affects chest"
"Work affects nose"
"Work affects chest or nose"
Total assessed
Symptoms are defined
*A subset of exposure rank 6 or more.

Table 2 Characteristics of study population by exposure rank. (Percentages in parentheses are based on fewer than 25 subjects)

	Percentage in given exposure rank				Intermittent exposure group	
	Main group				5	7*
	Never ≥ 6	Past ≥ 6 only	Current ≥ 6	Total		
Sex: Male	39	72	73	55	(100)	100
Age (y): <25	24	13	34	25	(16)	100
25-44	36	56	31	38	(53)	0
≥ 45	40	31	34	37	(32)	0
Years employed in bakery:						
<2	28	0	23	22	(5)	92
2-10	47	59	56	52	(63)	8
>10	25	41	21	26	(32)	0
Smoking status:						
Current smoker	47	59	54	51	(63)	23
Ex-smoker	17	26	11	17	(21)	0
Never smoked	36	15	34	32	(16)	77
Atopic	41	38	30	37	(50)	62
Total assessed	125	39	234	19	26	

*A subset of exposure rank 7.

Table 3 Symptoms reported by exposure rank. (Percentages in parentheses are based on fewer than 25 subjects)

Symptoms	Percentage in exposure rank				Intermittent exposure group	
	Main group				5	7*
	Never ≥ 6	Past ≥ 6 only	Current ≥ 6	Total		
Chronic bronchitis	6	23	21	13	(5)	0
Dyspnoea	17	28	19	19	(0)	8
Wheeze:						
Any	19	36	26	24	(21)	23
Work related	6	10	13	9	(5)	0
Chest tightness:						
Any	14	33	21	20	(16)	8
Work related	5	8	7	7	(5)	0
Difficulty in breathing:						
Any	12	23	17	16	(12)	8
Work related	4	8	9	6	(0)	0
Any chest symptoms:						
Any	31	51	35	35	(28)	23
Work related	9	6	17	13	(11)	0
Nasal symptoms:						
Any	27	46	54	38	(32)	46
Work related	13	20	30	19	(21)	8
Any chest or nasal symptoms:						
Any	46	72	57	54	(37)	62
Work related	17	33	36	25	(26)	8
"Work affects chest"	2	18	15	8	(0)	6
"Work affects nose"	7	27	30	17	(11)	12
"Work affects chest or nose"	8	40	32	21	(11)	12
Total assessed	125	39	70	234	19	26

Symptoms are defined in the text.

*A subset of exposure rank 7.

Table 4 Standardised FEV₁/FVC ratio, PD₂₀, and results of skin prick test to any bakery antigen by exposure rank. (Percentages in parentheses are based on fewer than 25 subjects)

	Percentage in exposure rank				Intermittent exposure group	
	Main group				5	7*
	Never ≥ 6	Past ≥ 6 only	Current ≥ 6	Total		
Standardised (FEV ₁ /FVC) $\times 100$:						
<70	6	11	14	9	(19)	5
70-	28	42	39	33	(38)	32
80-	58	42	42	51	(44)	50
90-	8	6	5	7	(0)	14
Total assessed	103	36	57	201	16	22
PD ₂₀ (mcmmol):						
>120	74	64	58	68	(53)	71
30-120	15	11	24	17	(6)	29
<30	11	25	19	15	(41)	0
Total assessed	113	36	59	208	17	24
Skin prick test positive, any bakery antigen	28	54	35	35	(50)	58
Total assessed	118	39	60	217	18	24

*A subset of exposure rank 7.

employed in the bakery for between two and 10 years and further 26% for more than 10 years. About one third of the workers in the main group had never smoked, 42% of the women and 23% of the men. By contrast, 77% of the Saturday part time workers had never smoked.

RESPIRATORY SYMPTOMS

For each of the exposure ranks within the main group the prevalence of most symptoms was similar for men and women, therefore the results for both sexes have been tabulated together (table 3). Chronic bronchitis was reported by 13% of the main group, the proportion increased with increasing exposure category. Dyspnoea was more common among women (25%) than among men (14%) and was not associated with increasing exposure.

Thirty five per cent of the workers in the main group reported one or more chest symptoms (wheeze, chest tightness, or difficulty in breathing), 13% had work related symptoms—that is, their symptoms were better when they were away from work—and 8% considered that working in the bakery affected their chest. Nasal symptoms (sneezing or an itchy or runny nose) were common; they were reported by 38% of the main group and about half were work related. In all, 25% of those in the main group reported work related chest or nasal symptoms, the proportion being highest among those currently (36%) or previously (33%) in exposure rank 6 or above.

Of those in the intermittent exposure group, the

Table 5 Results of logistic regression analyses*

Dependent variable	Significant independent variable(s)	Regression coefficient (SE)	Constant term (SE)	Interpretation	
				Change	Increase in odds ratio
Chronic bronchitis	Ever ≥ 6 exposure	1.66 (0.48)	-2.92 (0.42)	Ever v never ≥ 6 exposure	4.1
Dyspnoea	Female sex†	1.03 (0.37)	-3.78 (0.76)	Female v male	2.8
	Ever smoked	1.08 (0.44)		Ever v never smoked	2.9
Work related chest symptoms	Current exposure rank	0.14 (0.07)	-2.38 (0.35)	Increase of one exposure rank	1.2
Work related nasal symptoms	Current exposure rank	0.25 (0.06)	-1.01 (0.57)	Increase of one exposure rank	1.3
	Age	-0.04 (0.01)		Increase of 10 years	0.7
Work related chest or nasal symptoms	Current exposure rank	0.22 (0.06)	-1.79 (0.06)	Increase of one exposure rank	1.2
PD ₂₀ < 30 mcml	Ever ≥ 6 exposure	0.84 (0.40)	-2.13 (0.30)	Ever v never ≥ 6 exposure	2.3
Positive skin test to one or more bakery antigens	Atopic	2.79 (0.39)	-2.89 (0.42)	Atopic v non-atopic	16.3
	Ever ≥ 6 exposure	1.10 (0.38)		Ever v never ≥ 6 exposure	3.0
	Years worked in bakery	0.06 (0.022)		Additional 10 years in the bakery	1.8

*Based on workers in the main exposure group.

†Male = 1, female = 2.

proportion reporting symptoms was generally lower than for those in the main group. This was particularly true for the subset of exposure group 7 (the Saturday cleaning workers), none of whom had chronic bronchitis or work related chest symptoms, although 23% had wheeze which was not work related. Nevertheless, 12% considered that work affected their nose or chest.

The stepwise multiple logistic regression analysis identified a measure of exposure as the most significant independent factor associated with symptoms with the exception of dyspnoea which was most common in women and was also associated with a history of smoking (table 5).

PULMONARY FUNCTION TESTS

The regression coefficients for FEV₁ against age for men and women aged 25 or more combined were approximately 0.03 l/year both for smokers and non-smokers. The standardised FEV₁ for men was not related to any measure of exposure whereas women who had worked at some time in exposure rank 6 or more had significantly lower FEV₁ than those who had not.

The standardised FEV₁/FVC ratio tended to decrease with increasing exposure rank (table 4), the proportion of workers with a ratio less than 80% increasing from 34% in those never exposed at rank 6 or more to 53% in those currently in exposure rank 6-10. One third of the workers had measurable bronchial reactivity (PD₂₀ ≤ 120 mcml) (table 4), the proportion within the main group increasing from 26% in those never exposed at rank 6 or more to 42% of those currently in exposure rank 6-10.

The stepwise linear regression analysis of the age standardised FEV₁/FVC ratio isolated sex and current smoking as the only two significant factors. The ratio was lower in men (average 4.3% less than women) and current smokers (average 2.4% less than current non-

smokers). A PD₂₀ of 30 mcml or less was significantly associated with ever having been exposed at rank 6 or higher (table 5).

SKIN TESTS

Forty per cent of the workers (44% of the men and 34% of the women) had a positive skin test to one or more common allergens, the commonest being *D pteronyssinus* (30%) (table 6). A third had a positive test to one or more grain mites and there was a high degree of concordance in the results for the five grain mites. Of the 77 workers with a positive skin test to *D pteronyssinus*, 77% were positive to one or more grain mites compared with only 14% of those with a negative skin test to *D pteronyssinus* ($p < 0.001$). Positive skin tests to one or more of the other bakery allergens occurred in 9%, reactions to *A fumigatus*.

Table 6 Results of skin prick tests

Positive to	No positive	%	
Common allergens:			
<i>Dermatophagoides pteronyssinus</i>	77	30	40
Cat fur	67	26	
B2 grass pollen	48	18	
Grain mites:			
<i>Tyrophagus longior</i>	62	24	33
<i>Glycyphagus destructor</i>	59	23	
<i>Acarus siro</i>	58	22	
<i>Glycyphagus domesticus</i>	46	18	
<i>Tyrophagus putrescentiarum</i>	45	17	
<i>Tribolium confusum</i> (flour beetle)	28	11	38
Other bakery allergens:			
Mixed flour	14	5	
Wheat grain	9	4	
Mould mix	6	2	
Bakers' yeast	3	1	
<i>Aspergillus fumigatus</i>	1	<1	
Total assessed	259	100	

Respiratory

bakers y less).

There common proportion in those (table 4) allergens was associated response In the to one of atopy, a the num

Discussion

Total di producti exceeded ingredier They we areas. T independ the work The mea ers who variabili longer pe useful pr

Work by this v flour was the subje subjects There w piratory bronchia significant exposure Proba

responsi some of t tion. Son likely to l studies h but othe response the natu

This t subjects employr reduce t since ato associate of atopy.

bakers yeast, and mould mix being uncommon (2% or less).

There was no relation between positive reactions to common allergens and exposure to dust. The highest proportion of positive responses to bakery antigen was in those with a history of exposure in rank 6 or more (table 4). A high proportion of reactions to common allergens in the intermittent exposure subset of group 7 was associated with a high proportion of positive responses to grain mites and other bakery antigens.

In the logistic regression analysis positive skin test to one or more bakery antigens was associated with atopy, a history of exposure in rank 6 or higher, and the number of years worked in the bakery (table 5).

Discussion

Total dust concentrations were measured in the production areas of this bakery and several samples exceeded the exposure limit for nuisance dust in the ingredients preparation and manufacturing areas. They were much lower in the wrapping and despatch areas. These objective measurements supported the independently derived ranking system used to classify the workforce for exposure according to job category. The measurements in cleaning and maintenance workers who were intermittently exposed showed great variability and much larger numbers of samples over longer periods would have been necessary to produce a useful profile of exposure in these subjects.

Work related symptoms were reported frequently by this workforce and sensitivity to components of flour was shown by skin prick tests in over a third of the subjects. Both were found to be more common in subjects with higher levels of bakery dust exposure. There was also evidence of exposure related respiratory effects from measurements of non-specific bronchial reactivity. By contrast, FEV₁/FVC ratio was significantly related to sex and smoking but not to exposure, being lowest in men and current smokers.

Probably one or more allergens in wheat flour are responsible for the skin test responses and at least some of the respiratory effects observed in this population. Some symptoms, however, particularly nasal, are likely to be due to simple non-specific irritation. Other studies have implicated IgE in the asthma of bakers^{12,13} but other immunological¹ and non-immunological¹⁴ responses may also operate. Further work dissecting the nature of the response is required.

This bakery has a selection policy of excluding subjects with current symptomatic asthma from employment. This selection may have been expected to reduce the numbers of atopic subjects in the study, since atopic status and bronchial hyperreactivity are associated in the general population.¹⁵ The prevalence of atopy, however, was similar to that of the general

population.¹⁶ It was thought that the high prevalence of grain mite skin positivity might have resulted from cross reactivity with house dust mite but recent studies have found no such cross reactivity.²¹⁻²³ In the present study a positive skin test response to grain mites was related to exposure variables whereas a response to *D pteronyssinus* was not. This finding is being explored further. The relation of skin test responsiveness to bakery antigens with duration of exposure is consistent with the previous finding in an Australian bakery²⁴ and with a prospective study of skin test responses conducted over five years.¹⁰ It indicates that continued exposure results in development of sensitisation to bakery dust components.

The present study has shown that even in a modern bakery control of dust exposure presents a continuing problem. Bakery dust concentrations exceeded the exposure limit for nuisance dust at some times in some areas and sensitisation of workers had occurred as measured by skin test responses to bakery antigens. Respiratory symptoms, non-specific bronchial reactivity, and skin responses were related to exposure to bakery dust.

The help of the bakery management and staff and the Bakers' Union in the conduct of the study is gratefully acknowledged. Exposure rankings were determined by Dr P Harries and Mr B Tolley. Mrs J K Wilson and Mrs P A M Williamson helped with the air sampling. Secretarial help was provided by Miss Cathi Gray, Ms Elizabeth Bingle, Miss Carole Easton, Miss Elizabeth Corrigan, and Miss Aine Walsh.

References

- 1 Anonymous. Bakers' asthma. *Br Med J* 1981;282:678.
- 2 Pritchard MG, Ryan G, Musk AW. Wheat flour sensitisation and airways disease in urban bakers. *Br J Ind Med* 1984;41:450-4.
- 3 Pritchard MG, Ryan G, Walsh BJ, Musk AW. Skin test and RAST responses to wheat and common allergens and respiratory disease in bakers. *Clin Allergy* 1985;15:203-10.
- 4 Walsh BJ, Wrigley CW, Musk AW, Baldo BA. A comparison of the binding of IgE in the sera of patients with bakers' asthma to soluble and insoluble wheat-grain proteins. *J Allergy Clin Immunol* 1985;76:23-8.
- 5 Klaustermeyer WB, Bardana EJ Jr, Hale FC. Pulmonary hypersensitivity to alternaria and aspergillus in bakers' asthma. *Clin Allergy* 1977;7:227-33.
- 6 Popescu IG, Ulmeanu V, Murariu D. Atopic and non-atopic sensitivity in a large bakery. *Allergol Immunopathol* 1981;9:307-12.
- 7 Frankland AW, Lunn JA. Asthma caused by the grain weevil. *Br J Ind Med* 1965;22:157-9.
- 8 Baur X, Fruhmman G, Haug B, Rasche B, Reicher W, Weiss W. Role of aspergillus amylase in baker's asthma. *Lancet* 1986;i:43.
- 9 Thiel H, Ulmer WT. Bakers' asthma: development and possibility for treatment. *Chest* 1980;78 (suppl):400-3.
- 10 Herschheimer H. The skin sensitivity to flour of bakers' apprentices. *Acta Allergol* 1973;28:42-9.
- 11 James AL, Cookson WOCM, Butlers G, et al. Symptoms and

- longitudinal changes in lung function in young seasonal grain handlers. *Br J Ind Med* 1986;43:587-91.
- 12 Jarvinen KAJ, Pirila V, Björkstén F, Keskinen H, Lintinen M, Stubb S. Unsuitability of bakery work for a person with atopy: a study of 234 bakery workers. *Ann Allergy* 1979;42:192-5.
 - 13 Napolitano J, Weiss NS. Occupational asthma of bakers. *Ann Allergy* 1978;40:258-61.
 - 14 Olenchock SA, Mull JC, Major PC. Extracts of airborne grain dusts activate alternative and classical complement pathways. *Ann Allergy* 1980;44:23-8.
 - 15 Health and Safety Executive. *Occupational exposure limits*. London: HMSO, 1986. (HSE guidance notes EH40.)
 - 16 American Thoracic Society statement. Snowbird workshop on standardization of spirometry. *Am Rev Respir Dis* 1979;119:831-8.
 - 17 Yan K, Salome C, Woolcock AJ. Rapid method for measurement of bronchial responsiveness. *Thorax* 1983;38:760-5.
 - 18 Armitage P, Berry G. *Statistical methods in medical research*. 2nd ed. Oxford: Blackwell, 1987.
 - 19 Cockcroft DW, Murdock KY, Berscheid BA. Relationship between atopy and bronchial responsiveness to histamine in a random population. *Ann Allergy* 1984;53:26-9.
 - 20 Witt C, Stuckey MS, Woolcock AJ, Dawkins RL. Positive allergy prick tests associated with bronchial histamine responsiveness in an unselected population. *J Allergy Clin Immunol* 1986;77:698-702.
 - 21 Korsgaard J, Dahl R, Iversen M, Hallas T. Storage mites as a cause of bronchial asthma in Denmark. *Allergol Immunopathol* 1985;13:143-9.
 - 22 Georges P, Delvine A, de Montis G, Rast et A C Cariens desdenrées entreposées. *Allergie Immunol* 1987;19:393-7.
 - 23 Van Hage-Hamsten M, Johansson SGO, Johansson E, Widen A. Lack of allergenic cross-reactivity between storage mites and dermatophagoides pteronyssinus. *Clin Allergy* 1987;17:23-31.

Vancouver style

All manuscripts submitted to the *Br J Ind Med* should conform to the uniform requirements for manuscripts submitted to biomedical journals (known as the Vancouver style).

The *Br J Ind Med* together with many other international biomedical journals, has agreed to accept articles prepared in accordance with the Vancouver style. The style (described in full in *Br Med J*, 24 February 1979, p 532) is intended to standardise requirements for authors.

References should be numbered consecutively in the order in which they are first mentioned in the text by Arabic numerals above the line on each occasion the reference is cited (Manson¹ confirmed other reports^{2,3}...). In future references to papers submitted to the *Br J Ind Med* should include: the names of all authors if there

are six or less or, if there are more, the first three followed by *et al*; the title of journal articles or book chapters; the titles of journals abbreviated according to the style of *Index Medicus*; and the first and final page numbers of the article or chapter.

Examples of common forms of references are:

- 1 International Steering Committee of Medical Editors. Uniform requirements for manuscripts submitted to biomedical journals. *Br Med J* 1979;1:532-5.
- 2 Soter NA, Wasserman SI, Austen KF. Cold urticaria: release into the circulation of histamine and eosinophil chemotactic factor of anaphylaxis during cold challenge. *N Engl J Med* 1976;294:687-90.
- 3 Weinstein L, Swartz MN. Pathogenic properties of invading micro-organisms. In: Sodeman WA Jr, Sodeman WA, eds. *Pathologic physiology: mechanisms of disease*. Philadelphia: W B Saunders, 1974:457-72.

Rena solvei

J M HAR
J A WAT

From the J
Edgbaston.

ABSTRACT
occupatio
nephritis.
possibiliti
were com
place of i
proved ca
reviewed
referents
environme
semiquant
different s
renal canc
fourfold e
other pub

During the
been paid
exposure t
reports tha
link betwe
results of s
Research in
types of ki
nephritis.

In this re
the case ref
be reported
glomerulor
disease thes
of case rel
studies wen
the very na
may well ur
case refere
almost with
flaws. The
Regional C

Accepted 31 O

Occupational Disease Surveillance: Occupational Asthma

In 1987, the National Institute for Occupational Safety and Health (NIOSH), CDC, initiated the Sentinel Event Notification System for Occupational Risks (SENSOR) (1), a pilot project conducted in association with state health departments. A goal of SENSOR is to improve the reporting and surveillance of work-related health conditions, including occupational asthma. Of the 10 states* participating in the SENSOR

*California, Colorado, Massachusetts, Michigan, New Jersey, New York, Ohio, Oregon, Texas,

Occupational Asthma – Continued

program, six (Colorado, Massachusetts, Michigan, New Jersey, New York, and Wisconsin) have identified occupational asthma as a condition targeted for surveillance. This report describes the implementation and early results of occupational asthma surveillance in Michigan, Colorado, and New Jersey, whose programs share certain features.

SENSOR programs in each of these three states receive occupational asthma case reports by telephone from any health-care provider in the respective state. Information about the surveillance activity has been disseminated to groups of "sentinel providers" (such as allergists and pulmonary and occupational medicine specialists) who are most likely to encounter occupational asthma in their clinical practices. Characteristics of the case report (including its congruence with the surveillance case definition [see box], the number of co-workers with exposures similar to those of the reported case-patient, and the number of co-workers with respiratory symptoms) determine priorities for follow-up workplace investigations conducted by the SENSOR program personnel. Each program sends to reporting physicians summaries of worksite investigations conducted in response to cases they have reported. To assist physicians in the evaluation of possible cases, the programs may provide other services such as peak flow meters (New Jersey and Colorado) or radioallergosorbent testing (Michigan). In addition, all three programs actively collaborate with academic occupational medicine programs in their states.

Michigan. In Michigan, an occupational disease reporting law was already in effect when the SENSOR program started. With the implementation of SENSOR, physician-education efforts and case follow-up were enhanced and focused on a few target conditions, including occupational asthma. Consequently, the number of occupational asthma reports increased sharply, from 18 during 1984–1986 to 101 cases reported from September 1988 through August 1989. Cases have been reported in persons who worked in a variety of exposure settings, and case follow-ups have led to the recognition of at least one new setting for occupational asthma—sugar beet pulp processing. Thus far, at eight worksites where investigations have been completed or are in progress, employee interviews have identified 97 co-workers of reported patients with symptoms suggestive of occupational asthma.

Colorado. In Colorado, voluntary reporting of occupational asthma cases started in October 1987; in August 1988, state health regulations were modified to make occupational asthma and occupational hypersensitivity pneumonitis reportable conditions. From October 1987 through December 1989, Colorado SENSOR received 87 case reports of occupational asthma and 21 case reports of hypersensitivity pneumonitis. In Colorado, the SENSOR program gives health-care providers a mechanism to report unusual clusters of occupational illness. For example, from two case reports received in Colorado, a cluster of 14 cases of probable hypersensitivity pneumonitis was identified among workers at an indoor swimming pool; follow-up investigation is under way.

New Jersey. New Jersey implemented voluntary reporting of occupational asthma in 1988. From June 1988 through October 1989, the New Jersey SENSOR program received reports of 66 possible cases of occupational asthma. Seven of the first eight worksites investigated had inadequate engineering controls; at these sites, 35 co-workers of possible case-patients had work-related respiratory symptoms.

*Occupational Asthma – Continued***SURVEILLANCE GUIDELINES FOR STATE HEALTH DEPARTMENTS:
OCCUPATIONAL ASTHMA****REPORTING GUIDELINES**

State health departments should encourage providers to report all suspected or diagnosed cases of occupational asthma. These should include persons with:

- A. A physician diagnosis of asthma
AND
- B. An association between symptoms of asthma and work.

State health departments should collect appropriate clinical, epidemiologic, and workplace information on reported cases to set priorities for workplace investigations.

SURVEILLANCE CASE DEFINITION

- A. A physician diagnosis of asthma*
AND
- B. An association between symptoms of asthma and work[†] and any one of the following:
 - 1. Workplace exposure to an agent or process previously associated with occupational asthma[‡]
OR
 - 2. Significant work-related changes in FEV1 or PEF[§]
OR
 - 3. Significant work-related changes in airways responsiveness as measured by nonspecific inhalation challenge[¶]
OR
 - 4. Positive response to inhalation provocation testing with an agent to which patient is exposed at work. Inhalation provocation testing with workplace substances is potentially dangerous and should be performed by experienced personnel in a hospital setting where resuscitation facilities are available and where frequent observations can be made over sufficient time to monitor for delayed reactions.

*Asthma is a clinical syndrome characterized by increased responsiveness of the tracheo-bronchial tree to a variety of stimuli (2). Symptoms of asthma include episodic wheezing, chest tightness, and dyspnea, or recurrent attacks of "bronchitis" with cough, sputum production, and rhinitis (3). The primary physiologic manifestation of airways hyper-responsiveness is variable or reversible airflow obstruction, which may be demonstrated by significant changes in the forced expiratory volume in 1 second (FEV1) or peak expiratory flow rate (PEFR). Airflow changes can occur spontaneously, with treatment, with a precipitating exposure, or with diagnostic maneuvers such as nonspecific inhalation challenge.

[†]Patterns of association can vary. The following examples are patterns that may suggest an occupational etiology: symptoms of asthma develop after a worker starts a new job or after new materials are introduced on a job (a substantial period of time may elapse between initial exposure and development of symptoms); symptoms develop within minutes of specific activities or exposures at work; delayed symptoms occur several hours after exposure, during the evenings of workdays; symptoms occur less frequently or not at all on days away from work and on vacations; symptoms occur more frequently on returning to work. Work-related changes in medication requirements may have similar patterns, also suggesting an occupational etiology.

[‡]Many agents and processes have been associated with occupational asthma (3,4), and others continue to be recognized.

[§]Changes in nonspecific bronchial hyperreactivity can be measured by serial inhalation challenge testing with methacholine or histamine. Increased bronchial reactivity (manifested by reaction to lower concentrations of methacholine or histamine) following exposure and decreased bronchial reactivity after a period away from work are evidence of work-relatedness.

Occupational Asthma – Continued

Reported by: RE Hoffman, MD, State Epidemiologist, Colorado Dept of Health. KD Rosenman, MD, College of Human Medicine, Michigan State Univ, East Lansing; F Watt, Michigan Dept of Public Health. M Stanbury, MSPH, New Jersey Dept of Health. Div of Respiratory Disease Studies and Office of the Director, National Institute for Occupational Safety and Health, CDC.

Editorial Note: Asthma caused by occupational exposures has been recognized for nearly 3 centuries (3), but the true incidence and prevalence of work-induced asthma remain uncertain. More than 200 agents have been associated with workplace asthma (5), and the classes of agents implicated include certain microbial products (e.g., *Bacillus subtilis* enzymes in the detergent industry), certain animal proteins (e.g., urine protein/dander from laboratory mammals), certain plant products (e.g., wheat flour), and certain industrial chemicals (e.g., toluene diisocyanate). Occupational asthma is an increasingly important cause of respiratory impairment; it can persist for years, even after termination of workplace exposures (6). Early recognition is particularly important because a more favorable prognosis is associated with a shorter duration of symptoms before diagnosis (7) and because prompt removal from further exposures to the offending agent is beneficial. Fatal cases have been reported when workplace exposures continue (8). Identification of occupational asthma can also lead to recognition of affected co-workers, identification and correction of inadequate worksite exposure controls, and discovery of new causes of occupational asthma (9).

Early experience in Michigan, Colorado, and New Jersey indicates that physician reporting of occupational asthma can be used to identify workplaces with remediable health hazards. This approach may improve surveillance of occupational asthma and provide opportunities for primary and secondary prevention.

To facilitate provider-based surveillance of work-related conditions and to enhance uniformity of reporting in the states, NIOSH periodically disseminates recommended surveillance case definitions for selected occupational diseases and injuries. Because these definitions are designed for surveillance-related functions, they may differ from those used for other purposes, such as determining workers' compensation or level of disability. The reporting guidelines and case definition for surveillance for occupational asthma[†] (see box) are recommended for surveillance of work-related asthma by state health departments receiving reports of cases from physicians and other health-care providers.

References

1. Baker EL. SENSOR: the concept. *Am J Public Health* 1989;79(suppl):18-20.
2. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. *Am Rev Respir Dis* 1987;136:225-44.
3. Chan-Yeung M, Lam S. Occupational asthma. *Am Rev Respir Dis* 1986;133:686-703.
4. Salvaggio JE, Taylor G, Weill H. Occupational asthma and rhinitis. In: Merchant JA, ed. *Occupational respiratory diseases*. Cincinnati: US Department of Health and Human Services, Public Health Service, CDC, 1986; DHHS publication no. (NIOSH)86-102.
5. Newman-Taylor AJ. Occupational asthma. *Thorax* 1980;35:241-5.

[†]This definition was reviewed and approved by a panel of consultants convened by NIOSH that comprise the Surveillance Subcommittee of the NIOSH Board of Scientific Counselors: H Anderson, MD, Wisconsin Department of Health and Social Services; M Cullen, MD, Yale University School of Medicine; E Eisen, ScD, Harvard School of Public Health; R Feldman, MD, Boston University School of Medicine; J Hughes, MD, University of California, San Francisco; MJ Jacobs, MD, University of California, Berkeley; K Kriess, MD, National Jewish Center for Immunology and Respiratory Medicine; J Melius, MD, New York State Department of Health; J Peters, MD, University of Southern California School of Medicine; D Wegman, MD, University of Lowell.

Occupational Asthma — Continued

6. Chan-Yeung M. Evaluation of impairment/disability in patients with occupational asthma. *Am Rev Resp Dis* 1987;135:950-1.
7. Chan-Yeung M, Lam S, Koener S. Clinical features and natural history of occupational asthma due to Western Red Cedar. *Am J Med* 1982;72:411-5.
8. Fabbri LM, Danielli D, Crescioli S, et al. Fatal asthma in a subject sensitized to toluene diisocyanate. *Am Rev Resp Dis* 1988;137:1494-8.
9. Smith AB, Castellan RM, Lewis D, Matte T. Guidelines for epidemiologic assessment of occupational asthma. *J Allergy Clin Immunol* 1989;84:794-805.

Wheat flour sensitisation and airways disease in urban bakers

M G PRICHARD, G RYAN, AND A W MUSK

From the Department of Respiratory Medicine, Sir Charles Gairdner Hospital, Nedlands, Western Australia 6009

ABSTRACT A total of 176 bakers and 24 subjects employed as bread slicers and wrappers were studied to examine the effect of occupational category on respiratory symptoms, ventilatory capacity, non-specific bronchial reactivity, and prick skin test responses to wheat and common allergens. Bakers had a greater prevalence of attacks of wheeze and dyspnoea and more frequently considered that work affected their chests than did slicers and wrappers. Bakers with a history of asthma with onset since starting work in a bakery had a greater prevalence of chronic cough and sputum, increased bronchial reactivity, and positive prick skin test responses to wheat and common allergens than other bakers. There was a significant association between the frequency of positive prick skin tests to wheat and common allergens, suggesting that prior atopy facilitates sensitisation to cereal antigens. The frequency of positive prick skin responses to common allergens, however, declined with increasing baking duration whereas the frequency of positive skin responses to wheat increased with increasing baking duration, suggesting that subjects who were sensitised to common allergens were leaving the industry whereas subjects who stayed in the industry increased their risk of developing sensitisation to wheat. Oven handlers had a greater prevalence of attacks of wheeze and dyspnoea and more frequently considered that work affected their chests than either dough makers or general bakers. They also had a greater prevalence of positive prick skin test responses to wheat than dough makers or general bakers. Oven handlers also had a lower mean standardised casual FEV₁ than either general bakers or dough makers. Thus oven handlers appear to have a greater risk of developing respiratory allergy and airflow obstruction than bakers in other occupational categories.

Rhinitis and asthma are known to be related to baking.¹ Both have been shown to be IgE mediated² and numerous potential allergens have been implicated: wheat and other cereals,³⁻⁶ grain weevil,⁷ dust mite,⁸ *Alternaria* and *Aspergillus* organisms,⁹ and dough improvers.¹ Of these, wheat is the most frequently recognised source of antigen shown.¹⁰⁻¹¹ Sensitisation appears to be related to the intensity and duration of exposure in the industry¹ as well as to host factors such as a personal or family history of allergic respiratory disease.¹² Since the intensity of exposure to cereal flour may vary in different areas of the bakery,¹ job assignment in the bakery may possibly determine the level of exposure and thus

the prevalence rates of indices of respiratory disease. We examined the prevalence rates of respiratory symptoms, positive skin test responses to cereals and common allergens, impairment of ventilatory capacity, and increased non-specific bronchial reactivity in metropolitan bakers in Perth, Western Australia. In order to determine which exposure factors relate to the rates of respiratory disease, the measures of disease were examined in different occupational subgroups and in relation to duration of employment.

Subjects

We studied 200 men from 18 metropolitan bakeries. They included 176 bakers and 24 subjects employed only in slicing and wrapping bread. They rep-

Wheat
resente
tan are
bread
decline
exclud
and 22
analysis
(range
(range
was 39
was 17
Subj
assignm
most of
in three
categor
of ingr
and "s
small
bakeric
process
examin
indices
dough
in their
compar
dients
involve
many p

Method

All bak
(4-8 ar
their w
middle
mer.

RESPIR
All sul
questio
Resear
sympto
also ob
cough
three p
tive ye
recorde
questio
of brea
believ
chests"
cian tha
asthma
asthma
of asthr

represented 90% of all bakers in the Perth metropolitan area. Bakery employees engaged only to deliver bread were not included. Sixteen eligible subjects declined to participate in the study and two were excluded due to incomplete data. One female baker and 22 female bread slicers were excluded from analysis. The mean age of the bakers was 35.2 years (range 15-64) and the mean height was 174.8 cm (range 152-194). The mean age of the bread slicers was 39.6 years (range 23-58) and the mean height was 173.5 cm (range 161-194).

Subjects were classified according to their job assignments in the bakeries. At the time of the study most of the bakers (68%) worked in specialist tasks in three large automated bakeries. They were categorised as "manager or supervisor," "preparer of ingredients," "dough maker," "oven handler," and "slicer and wrapper." Other bakeries were small and less automated. Employees in such bakeries were involved in all aspects of the baking process and were classified as "general bakers." To examine the effect of occupational subgroups on indices of respiratory disease only general bakers, dough makers, and oven handlers who had worked in their current specialty for at least five years were compared. Dough makers and preparers of ingredients were combined because both groups were involved in product preparation for baking and many performed both tasks.

Methods

All bakers were tested at about the same time of day (4-8 am) at their place of work towards the end of their working shift. Studies were performed in the middle of the working week during spring and summer.

RESPIRATORY SYMPTOMS

All subjects completed a physician administered questionnaire based on the British Medical Research Council questionnaire on respiratory symptoms.¹² A detailed occupational history was also obtained. "Chronic bronchitis" was defined as cough productive of sputum on most days for at least three months of each year for two or more consecutive years.¹² Attacks of wheeze and dyspnoea were recorded if subjects responded positively to the question: "Have you ever had attacks of shortness of breath with wheezing?" Bakers were asked if they believed "that work in the bakery had affected their chests" and if they had "ever been told by a physician that they had asthma." Those with a history of asthma were further subdivided into those with asthma since childhood and those in whom the onset of asthma had occurred only since they had started

baking. "Work related asthma" was defined as the presence of attacks of wheeze and dyspnoea in subjects who believed that work affected their chests. This group included all those subjects with physician diagnosed asthma that had started since they had become bakers. "Seasonal rhinitis" was recorded if subjects responded positively to the questions: "Do you often sneeze or get an itchy, running nose?" and "Do you get this more often during any particular season?"

PULMONARY FUNCTION

Forced expiratory volume in one second (FEV₁) and forced vital capacity were recorded on a dry bellows spirometer (Vitalograph). The mean of the best two measurements of FEV₁ from three technically satisfactory attempts after one or more practice attempts was taken for analysis and corrected to BTPS.¹³ Standardised FEV₁ values were calculated for each subject using the age and height regression of the whole group and correcting the measured volume to the mean age and height of all subjects.

Bronchial reactivity was assessed using doubling doses of methacholine aerosol administered every 90 seconds from a hand operated calibrated Devilbiss No 40 nebuliser. The starting dose was 0.04 μ mol in subjects with an FEV₁ less than 60% of the predicted value or a history of asthma and 0.15 μ mol for other subjects.¹⁴ The challenge was terminated when the FEV₁ fell by more than 20% from the initial (post saline) value or a total cumulative dose of 30 μ mol of methacholine had been administered. Reactivity was expressed as the cumulative dose producing a 20% fall in FEV₁ (PD₂₀).

Prick skin tests were performed with a range of baking related and common allergens. Extracts of whole wheat, rye, barley and oats, bakers' yeast, grass pollens, house dust, and animal danders were obtained from Hollister-Stier (Spokane, Washington). House dust mite (*Dermatophagoides pteronyssinus*) extract was obtained from the Australian Commonwealth Serum Laboratories and wheat flour extracts from the Wheat Research Institute of the Australian Commonwealth Scientific and Industrial Research Organization. Histamine in a solution of 1 mg/ml (John Bull Laboratories, Victoria, Australia) was used as a positive control and the Hollister-Stier diluent as a negative control. The wheat flour extracts were supplied as a powder and made up to concentrations of 1 mg/ml and 0.1 mg/ml in 50% glycerine. For all skin tests a weal of 3 mm or more and greater than the negative control was measured as positive. "Atopy" was defined as the presence of a positive prick skin response to at least one common allergen.¹⁵

STATISTICAL METHODS

Continuous variables were compared using an unpaired *t* test. Comparisons of categorical variables used the chi-square test except if the expected values were less than five, when Fisher's exact test was used.¹⁴

Results

The group of 24 men employed as slicers and wrappers who had never worked as bakers were considered to be a suitable comparison group because they were less exposed to cereal flour by virtue of their assignment and location in the bakery. They were of similar age, height, and smoking habit to the 176 subjects employed directly in the baking process (table 1). There was a greater prevalence of attacks of wheeze and breathlessness in bakers and more

Table 1 Characteristics of bakers compared with those of slicers and wrappers

	Bakers	Slicers/wrappers
No	176	24
Mean age (y)	35	40
Smokers (%)	49	46
Ex-smokers (%)	20	29
Never smoked (%)	31	26
Chronic bronchitis (%)	25	8
Attacks of wheeze and dyspnoea (%)	20	4*
Work affected chest (%)	19	0**
Work related asthma (%)	5	0
Mean standardised FEV ₁ (l)	4.07	4.02
Increased bronchial reactivity (PD ₂₀ < 30 µmol) (%)	41	21
Prick skin test responses:		
Wheat flour (%)	15	4
Grasses (%)	22	17
House dust (%)	14	8

Statistical significance of difference between bakers and slicers and wrappers **p* < 0.05, ***p* < 0.01.

Table 2 Characteristics of bakers with work related asthma

	Work related asthma	Other bakers
No	20	156
Mean age (y)	32	34
Smokers (%)	45	49
Ex-smokers (%)	15	21
Never smoked (%)	40	30
Chronic bronchitis (%)	60***	21
Mean standardised FEV ₁ (l)	3.95	4.09
Increased bronchial reactivity (PD ₂₀ < 30 µmol) (%)	75***	37
Prick skin test responses:		
Wheat flour (%)	50***	10
Grasses (%)	35***	19
House dust (%)	35***	12

Statistical significance of difference between bakers with work related asthma and other bakers ****p* < 0.001.

Prichard, Ryan, and Musk

Table 3 Relationship between prick skin test responses to wheat and co-existing indices of common allergy

	Wheat prick skin test response	
	Positive (%)	Negative (%)
Positive prick skin test response to common allergens	69	35***
Seasonal rhinitis	35	15*

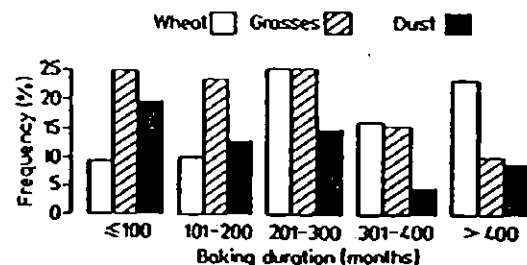
Statistical significance of difference between bakers according to their prick skin test response to wheat **p* < 0.05, ****p* < 0.001.

bakers believed that work affected their chests than slicers and wrappers. A similar proportion of bakers and slicers and wrappers had had asthma in childhood. None of the slicers and wrappers had developed asthma since starting work in the bakery.

Bakers tended to have increased bronchial reactivity (PD₂₀ < 30 µmol) and more positive prick skin test responses to wheat and other cereals than slicers and wrappers. These differences, however, were not statistically significant. There was a similar distribution of prick skin test responses to grasses and house dust in bakers and slicers and wrappers.

Twenty bakers fulfilled the definition of work related asthma. They were of similar age and smoking habit to other bakers (table 2). Sixty per cent of bakers with work related asthma fulfilled the criteria for chronic bronchitis, a significantly greater prevalence than in other bakers. Although there was no difference between the height and age standardised FEV₁ between the two groups, bakers with work related asthma more frequently had increased bronchial reactivity (PD₂₀ < 30 µmol) and positive prick skin tests to wheat flour and common allergens than other bakers.

There was a significantly greater prevalence of seasonal rhinitis and coexisting positive prick skin test responses to common allergens in bakers who reacted to wheat on skin testing than in those who did not react to wheat (table 3). There was also a positive relationship between duration of baking and frequency of positive prick skin test responses to



Frequency of positive prick skin responses to wheat, grasses, and house dust by duration of baking.

Wheat flour

Table 4 Skin test responses to wheat flour

No	Mean age (y)	Smokers (%)	Ex-smokers (%)	Never smoke	Attacks of wheeze and dyspnoea	Work affects chest	Prick skin test responses:
							Wheat flour (%)
							Grasses (%)
							House dust (%)
							Mean standardised FEV ₁ (l)
							Increased bronchial reactivity (PD ₂₀ < 30 µmol) (%)

Statistical significance **p* < 0.01.

wheat and positive prick skin test responses to house dust (figure 1).

The occurrence of attacks of wheeze and dyspnoea in bakers with work related asthma was significantly greater than in other bakers. Bakers with work related asthma also tended to have increased bronchial reactivity, positive prick skin test responses to wheat flour, and significant responses to house dust.

Discussion

In the bakery, the prevalence of asthma is high. The prevalence of asthma in bakers is significantly greater than in other bakers. The prevalence of asthma in bakers is significantly greater than in other bakers. The prevalence of asthma in bakers is significantly greater than in other bakers.

Table 4 Skin tests and pulmonary function in occupational subgroups

	Oven handlers	General bakers	Dough makers
No	16	29	17
Mean age (y)	49	44	41
Smokers (%)	44	59	53
Ex-smokers (%)	25	24	24
Never smoked (%)	31	17	24
Attacks of wheeze and dyspnoea (%)	44	14*	24
Work affects chest (%)	31	17	6*
Prick skin test responses:			
Wheat flour (%)	44	17	0**
Grasses (%)	38	17	12
House dust (%)	25	3	12
Mean standardised FEV ₁ (l)	3.54	4.05*	4.12***
Increased bronchial reactivity (PD20 < 30 µmols) (%)	56	41	29

Statistical significance of difference from oven handlers * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

wheat antigens in bakers, whereas the frequency of positive prick skin test responses to grasses and house dust decreased with increasing baking duration (figure).

The occupational subgroups were similar in age and smoking habit (table 4). Nevertheless, a group of 16 oven handlers had a greater prevalence of attacks of wheeze and breathlessness and more frequently considered that work in the bakery affected their chests than did a group of 29 general bakers or a group of 17 dough makers. Standardised FEV₁ was significantly lower in oven handlers than in dough makers or general bakers. Oven handlers also tended to have a greater prevalence of increased bronchial reactivity than general bakers and dough makers, although this was not statistically significant. Additionally, oven handlers more frequently reacted to wheat and other cereals on prick skin testing than dough makers.

Discussion

In the baking industry symptoms of work related asthma are common and appear to relate to exposure to ingredients of bread.¹⁰ Bakers more frequently admitted to attacks of wheeze and dyspnoea and considered that work affected their chests than slicers and wrappers. They showed a tendency towards a greater prevalence of positive prick skin test responses to wheat antigens, and those with work related attacks of wheeze and dyspnoea had a significantly greater prevalence of positive prick skin test responses to wheat antigens than other bakers. Pre-existing atopy may have predisposed the bakers to more frequent wheat flour sensitisation and respiratory disease than the less exposed slicers and wrappers.¹¹ Part of the excess frequency of positive

prick skin responses to common allergens may also be explained by cross reactivity between cereal and grass antigens.¹² Nevertheless the more obvious explanation for the findings is that bakers have work related allergic respiratory disease ("bakers' asthma").

Symptoms of wheeze and dyspnoea that were work related were associated with increased non-specific bronchial reactivity (though not with a lower standardised casual FEV₁). This result is in keeping with a previous study showing a higher frequency of positive acetylcholine tests in bakers with proved occupational disease than in unselected bakers or controls.⁹ Both studies support the concept that wheeze and dyspnoea are related to non-allergic bronchial reactivity in bakers' asthma as in other forms of allergen induced asthma.²⁰ The higher prevalence of positive skin tests to wheat in bakers with work related asthma indicates an association between exposure and symptoms and suggests that wheat is implicated in the pathogenesis of asthma in bakers.

The greater prevalence of seasonal rhinitis and co-existing positive prick skin test responses to common allergens in bakers who reacted to wheat on skin testing than in those who did not react to wheat supports earlier evidence that atopy may facilitate sensitisation to cereal antigens.¹² The frequency, however, of positive prick skin test responses to common allergens (grasses and house dust) declined with increasing duration of baking whereas the frequency of positive skin responses to wheat increased with increasing baking duration. Thus it appears that subjects with sensitivity to common allergens may be selectively leaving the industry (possibly because of the development of work related symptoms) whereas the surviving, less atopic population continues to develop sensitivity on exposure to wheat flour at work. A prospective study in the industry has been designed to evaluate this possibility.

Oven handlers had a greater prevalence of indices of respiratory disease than either dough makers or general bakers, despite the observation that dough-makers are more exposed to airborne, uncooked flour. The lower mean standardised FEV₁ was not explained by any difference in smoking habit. This may represent either the presence of industrial bronchitis with airflow obstruction or the result of recent occupational exposure to antigen in sensitised individuals.²¹ Since the measurement was a casual FEV₁ and not necessarily the best (postbronchodilator) value these data alone cannot distinguish between these two causes. The greater prevalence of other indices of disease in oven handlers, however, suggests that they may have exposure to more

potent allergens in wheat which are responsible for respiratory disease and skin reactivity. This may be attributed to alteration in respirability or antigenicity during cooking. Thus oven handlers may be at greater risk of developing symptoms and airflow obstruction at work than other bakers. Further attention should be paid to characterising the exposures of this group in efforts to control respiratory disease in bakers.

We thank the Bread Manufacturers' Association of Western Australia for its help with the conduct of the study and for meeting the costs of the skin testing materials. RAST measurements were performed by the Wheat Research Institute of the Australian Commonwealth Scientific and Industrial Research Organization, North Ryde, NSW, Australia. The help of Dr David Hoffman, Sr Sue Morey, and Sr Sandra Peach in collecting the data and Ms L Bingle and Ms A Pickard in the typing of the manuscripts is gratefully appreciated.

References

- ¹ Bonnevill P. Occupational allergy in bakery. In: Stenfort-Kroese WF, ed. *European Academy of Allergy, occupational allergy*. Springfield, Ill. C Thomas, 1958:161-8.
- ² Napolitano J, Weiss NS. Occupational asthma of bakers. *Ann Allergy* 1978;40:258-61.
- ³ Thiel H, Ulmer WT. Bakers' asthma: development and possibility for treatment. *Chest* 1980;78 (suppl):400-5.
- ⁴ Block G, Kijek K, Chan H, Tse KS, Chan-Yeung M. Pathogenic mechanisms in bakers' asthma. *Am Rev Respir Dis* 1982;125(suppl):74. (Abstract American Thoracic Society meeting.)
- ⁵ Herzheimer H. The skin sensitivity to flour of baker's apprentices. *Acta Allergol* 1973;28:42-9.
- ⁶ Hendrick DJ, Davies RJ, Pepys J. Bakers' asthma. *Clin Allergy* 1976;4:241-50.
- ⁷ Frankland AW, Lunn JA. Asthma caused by the grain weevil. *Br J Ind Med* 1965;22:157-9.
- ⁸ Popescu IG, Ulmeanu V, Muraniu D. Atopic and non-atopic sensitivity in a large bakery. *Allergol Immunopathol* 1981;9:307-12.
- ⁹ Klaustermeyer WB, Bardana EJ, Hale FC. Pulmonary hypersensitivity to alternaria and aspergillus in bakers' asthma. *Clin Allergy* 1977;7:227-33.
- ¹⁰ Anonymous. Bakers' asthma (Editorial). *Br Med J* 1981;282:678.
- ¹¹ Popa V, George SAJ, Gavanescu O. Occupational and non-occupational respiratory allergy in bakers. *Acta Allergol* 1970;25:159-77.
- ¹² Jarvinen KAJ, Pirila V, Bjorksten F, Kerstinen H, Lenninen M, Stubb S. Unsuitability of bakery work for a person with atopy: a study of 234 bakery workers. *Ann Allergy* 1979;42:192-5.
- ¹³ Douhuys A. *Breathing: physiology, environment and lung disease*. New York: Grune and Stratton; 1974:295-300, 307-13.
- ¹⁴ American Thoracic Society. Statement on definitions and classification of chronic bronchitis, asthma and pulmonary emphysema. *Am Rev Respir Dis* 1962;85:762-8.
- ¹⁵ Knudson RJ, Slatin RC, Lebowitz MD, Burrows B. The maximal expiratory flow-volume curve: normal standards, variability and the effects of age. *Am Rev Respir Dis* 1976;113:587-600.
- ¹⁶ Woolcock AJ, Yan K, Anderson SD, Stuckey M. Bronchial responsiveness in adult population. *Aust NZ J Med* (in press). (Abstract Thoracic Society of Australia Meeting.)
- ¹⁷ Woolcock AJ, Colman MH, Jones MW. Atopy and bronchial reactivity in Australian and Melanesian populations. *Clin Allergy* 1978;8:155-64.
- ¹⁸ Armitage P. *Statistical methods in medical research*. Oxford: Blackwell Scientific Publications, 1971.
- ¹⁹ Blands J, Diamant B, Kallos P, Kallos-Deffner L, Lowenstein H. Flour allergy in bakers. *Int Arch Allergy Appl Immunol* 1976;52:392-406.
- ²⁰ Mink JT, Gerrard JW, Cockerill DW, Cotton DJ, Dosman JA. Increased bronchial reactivity to histamine in nonsmoking grain workers with normal lung function. *Chest* 1980;77:28-31.
- ²¹ Chan-Yeung M, Wong R, MacLean L. Respiratory abnormalities among grain elevator workers. *Chest* 1979;75:461-7.

Prichard, Ryan, and Musk

Alp
coa.

J E BC

From the
the Dep

ABSTRU
miner:
and di
avera
lung f
may b
smoki
a grea
degre

Exposi
funcio
even i
pneum
This le
from c
related
dust w
this de
concer
major
centra
deficie
likelih
pheno
rare (
have r
with t
pheno
71%,
MM c
ity of
by ex
tion,
of α_1
dust c

Receiv
Accept

*Presen

Grain Dust Asthma

Presented by Kam S. Tse, M.D.

Workers exposed to grain dust include farmers, transport workers, and terminal elevator workers. In the United States, approximately 2 million farmers and 200,000 handling facility workers are exposed to grain dust annually. Grain includes wheat, barley, corn, soybean, rice, and sorghum. Barley produces the finest dust, which permeates the lung tissue more than other grain dust and is most irritating to the workers.

Tse cited a 1980 study in Vancouver and a 1984 study in Wisconsin and Minnesota in which grain workers reported symptoms of grain dust allergy in numbers of one-third and two-thirds, respectively. Grain dust is a mixture of materials such as cereal grain matter, fungi, insect mites, rodent matter, pollens, and insecticides. Dust levels of exposure vary greatly by the type of job and the season. The safe level of exposure or threshold limit value for inert dust has been determined to be 10 mg/m^3 of air. The mean exposure level for grain workers is 17.6 mg of respirable grain dust but cannot be regarded as inert dust.

Exposure over time to grain dust causes a decrease in lung function. A 6-year study showed statistically significant decreases in lung function, an average decrease of 31 ml of 1-second vital capacity annually. When lifetime nonsmokers are examined for obstructive airway disease, grain workers have more chronic bronchitis and wheezing. Over time, grain dust exposure has the same negative effect on lungs as smoking. Grain dust exposure coupled with smoking creates a synergistic effect on lung function. Tse noted that most of the grain workers studied were smokers.

In the laboratory, exposure of susceptible workers to grain dust extract produces immediate or late-phase allergic reactions. Inhalation provocation responses in the laboratory along with other data suggest that a

number of component allergens are present in the grain dust. While mites and fungi present in the grain dust are important components, they are not the major allergens, according to Tse.

An increased incidence of bronchial hyperreactivity in grain workers has been found. Three factors have been identified among workers with increased hyperreactivity: 1) allergy, 2) employment for over 5 years in the grain industry, and 3) abnormal lung function. Tse noted this created a vicious cycle. However, only 14% of grain workers develop bronchial hyperreactivity, so this does not explain all of the grain workers' symptoms.

The direct release of mediators from grain dust may be another mechanism to explain the pathogenesis of the symptom complex among grain workers. Between 6 and 30% of grain workers complain of "grain fever," which consists of muscle aches and elevated body temperature. Grain fever probably results from the direct release of mast cell mediators caused by the grain dust itself and does not involve an immunological response.

Tse summarized the clinical problems of grain workers as follows: high prevalence of bronchitis, including coughing, shortness of breath, nose and eye irritation, and airway obstruction; grain fever induced by the direct release of mediators from the lung tissue; and asthma (among 2 to 3% of workers) that involves an IgE antibody to the grain allergen. The major allergen in grain dust has not been isolated. It has been proposed to decrease the threshold limit value (TLV) from 10 to 4 mg/m^3 for grain dust exposure, although the real TLV has not been scientifically determined. In the opinion of the speaker, this can only be done by long-term surveys of grain workers in different locales with exposures to different levels of grain dust and with appropriate clinical correlations.

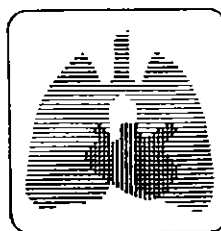
REFERENCES

1. Broder I, Mintz S, Huicheon M, et al. Comparison of respiratory variables in grain elevator workers and civic outside workers of Thunder Bay, Canada. *Am Rev Respir Dis*

- 119:193-203, 1979.
2. Chan-Yeung M, Schulzer M, MacLean L, Dorken E, Grzybowski S. Epidemiologic health survey of grain elevator workers in British Columbia. *Am Rev Respir Dis* 121:329-338, 1980.
3. Chan-Yeung M, Chan H, Salari H, Wall R, Tse KS. Grain dust extract induced direct release of mediators from human lung tissue. *J Allergy Clin Immunol* 80:279-284, 1987.
4. Corey P, Hutchison M, Broder I, Mintz S. Grain elevator workers show work-related pulmonary function changes and dose-effect relationships with dust exposure. *Br J Ind Med* 30:320-327, 1982.
5. DeLucca AJ, Godshall MA, Palmgren MS. Gram-negative bacterial endotoxins in grain elevator dusts. *Am Ind Hyg Assoc J* 45:336-339, 1984.
6. Desman J, Cotton D, Graham BC, Li KYR, Froh F, Barnett GD. Chronic bronchitis and decreased forced expiratory flow rates in lifetime nonsmoking grain workers. *Am Rev Respir Dis* 121:11-16, 1980.
7. doPico GA, Reddan W, Flaherty D, et al. Respiratory abnormalities among grain handlers—a clinical, physiologic and immunologic study. *Am Rev Respir Dis* 115:915-927, 1977.
8. doPico GA, Jacobs S, Flaherty D, Rankin J. Pulmonary reaction to durum wheat—a constituent of grain dust. *Chest* 81:55-61, 1982.
9. doPico GA, Flaherty D, Bhansali P, Chavaje N. Grain fever syndrome induced by inhalation of airborne grain dust. *J Allergy Clin Immunol* 69:435-443, 1982.
10. doPico GA, Reddan W, Tsiatis A, Peters ME, Rank J. Epidemiologic study of clinical and physiologic parameters in grain handlers of northern United States. *Am Rev Respir Dis* 130:759-765, 1984.
11. Enarson DA, Vedal S, Chan-Yeung M. Rapid decline in FEV₁ in grain handlers—relation to level of dust exposure. *Am Rev Respir Dis* 132:814-817, 1985.
12. Lewis DM, Romeo PA, Olenchock SA. Prevalence of IgE antibodies to grain and grain dust in grain elevator workers. *Environ Health Perspect* 66:149-153, 1986.
13. Manfreda J, Warren CPW. The effects of grain dust on health. *Rev Environ Health* 4:239-267, 1984.
14. Olenchock SA, Mull JC, Major PC, Peach MJ, Gladish ME, Taylor G. In vitro activation of the alternate pathway of complement by settled grain dust. *J Allergy Clin Immunol* 62:295-300, 1978.
15. Parnell CB, Jones DD, Ruthford RD, Goforth KJ. Physical properties of five grain dust types. *Environ Health Perspect* 66:183-188, 1986.
16. Tabona M, Chan-Yeung M, Enarson D, MacLean L, Dorken E, Schulzer M. Host factors affecting longitudinal decline in lung spirometry among grain elevator workers. *Chest* 85:782-786, 1984.
17. Tse KS, Warren P, Janusz M, McCarthy DS, Cherniack R. Respiratory abnormalities in workers exposed to grain dust. *Arch Environ Health* 27:74-77, 1973.
18. Warren P, Cherniack R, Tse KS. Hypersensitivity reactions to grain dust. *J Allergy Clin Immunol* 74:53:139-149. □

Acute Effects of Herbal Tea Dust Extracts on Lung Function*

*Eugenija Zuskin, M.D.; Bozica Kanceljak, M.D.;
Theodore J. Witek, Jr., Pharm.D.; and E. Neil Schachter, M.D., F.C.C.P.*



Vol. 96, p. 1327-1331
December 1989 Issue

Reprinted from CHEST

Acute Effects of Herbal Tea Dust Extracts on Lung Function*

Eugenija Zuskin, M.D.; Bozica Kanceljak, M.D.;

Theodore J. Wittek, Jr., Pharm.D.; and E. Neil Schachter, M.D., F.C.C.P.

The acute effect of herbal tea dust extracts on lung function was studied in 15 of 25 healthy subjects responding to the inhalation of these extracts. Bronchial inhalation challenge was performed with tea extracts (sage, dog rose and gruzyan) and with normal saline solution as a control substance to assess their baseline airway reactivity to an isotonic aerosol. Lung function testing was performed before exposure and at 0, 15, 30, and 60 minutes after the cessation of exposure. The same subjects were also tested by challenge with methacholine. Lung function was measured by recording FVC, FEV₁, FEF₅₀, FEF₂₅, SGaw, and

Raw. Subjects were skin tested by the skin prick method and serum IgE levels were determined. The findings suggested that neither baseline nonspecific airway reactivity nor specific markers of immediate sensitivity to tea predict airway responses to tea extracts. Further evaluation of immunologic markers may help to explain the onset and progression of airway disease in workers.

(Chest 1989; 96:1327-31)

PD20FEF₂₅ = provocative dose of methacholine causing a 20% decrease in the FEF₂₅; CBE = cotton bract extract

Tea is made from the young leaves and leaf buds of the tea plant, a species of evergreen. The principal chemical constituents of tea are caffeine, tannin and essential oil. One kilogram of tea may contain up to 30 g of caffeine. There are three main classes of tea: (1) fermented or black; (2) unfermented or green; and (3) the semifermented or oolong teas. Tea comes from practically the same plant in all countries, the differences in the various classes being due to methods of cultivation and manufacture, as well as local climatic and soil conditions.

There are a few published reports on the effects of herbal teas on respiratory function. Several authors have listed tea as a cause of occupational asthma.^{1,2} Castellani and Chalmers³ described "tea factory cough" in workers occupationally exposed to tea dust. Uragoda⁴ reported a case of tea maker's asthma caused by inhalation of tea fluff. Attacks of allergic disease were described by Ebihara⁵ in two workers employed in a tea garden and Mackay⁷ described a high prevalence of respiratory diseases in tea garden workers. In our previous study of tea workers, a significantly higher prevalence of chronic respiratory symptoms was found in tea workers than in control subjects.⁸ Similarly, Uragoda⁹ found a prevalence of chronic bronchitis and asthma in tea workers higher than that expected in the general population. Pulmonary function in tea

workers was studied by Al-Zuhair and Cinkotai¹⁰ and by Castellan et al,¹¹ who reported across shift reductions for FEV₁ in tea workers related to tea dust exposure. In our study of tea workers, we found acute reductions of ventilatory capacity that were greater in workers with positive skin tests to different tea dust allergens than in those with negative skin tests.¹² Increased levels of IgE in tea workers (20.9 percent) have been interpreted as indicative of allergen-induced respiratory reactions.¹³

In the present investigation, we studied the acute effect of the inhalation of different tea dust extracts on lung function in healthy subjects. The relationship of nonspecific airway reactivity to the response to tea dust inhalation was measured using methacholine provocation testing.

SUBJECTS AND METHODS

The study was performed in 15 of 25 healthy subjects (five men and ten women) characterized as responders to tea dust (see bronchoprovocation with tea dust extracts); age range 18 to 23 years. All tested subjects had never been occupationally exposed to any dusts or fumes. They were healthy volunteers without any history of atopic disease recruited from a University student population in Zagreb. All volunteers signed informed consent as approved by the University institutional review board.

Subjects were asked about respiratory and/or allergic symptoms, such as cough, phlegm, chest tightness, wheezing, shortness of breath, and allergy to dust, food, medication, metals, or insects. Before the bronchial challenge with tea extract, all subjects were asymptomatic and had normal lung function.

Lung function measurements were performed using a body plethysmograph. Ventilatory capacity was measured by recording maximum expiratory flow-volume (MEFV) curves from which the forced vital capacity (FVC), one-second forced expiratory volume (FEV₁), and maximum expiratory flow rates at 50 percent (FEF₅₀) and at the last 25 percent (FEF₂₅) of the vital capacity were read. In addition, airway resistance (Raw) and specific conductance

*From the Andrija Stampar School of Public Health, and the Institute for Medical Research and Occupational Medicine, Zagreb, Yugoslavia; and The Mount Sinai School of Medicine, New York.

This study was supported in part by grant No SPCF-FIC-493 from the National Institutes of Health, and by the Henry and Catherine Caissman and the Miller Foundations, New York.

Manuscript received December 28; revision accepted April 4.

Reprint requests: Dr. Schachter, Mt. Sinai Medical Center, One Gustave Levy Place, New York 10029

(SCaw) were calculated. Measured values were compared with expected normal values of CECA[®] for FVC and FEV₁, of Chermiack and Haber¹⁶ for FEF50 and FEF25, and of Uhmer et al¹⁷ for Raw and SCaw.

Bronchoprovocation and Skin Testing with Tea Dust Extracts

The present study was performed in 15 of 25 subjects selected because of their sensitivity to tea extracts. They were initially tested with tea extracts and with normal saline solution as a control substance. Two and one half milliliters of tea extract or normal saline solution was placed in a nebulizer which, with an airflow of 15 L/min, nebulized the fluid during inspiration only. The subjects continued to inhale the whole amount of the solution (tea extract or a placebo) during normal quiet breathing until the nebulizer was entirely empty. Each subject was challenged with all three tea extracts on separate days. Bronchoprovocation with tea extract and normal saline solution was performed at least one week apart. Tea extracts were prepared from three types of tea dust collected from operating machines in the work areas of industries previously studied.¹² The teas included in this study were sage, dog rose, and gruzyan. Aqueous extracts were prepared using 1 g of tea dust for 3 ml of sterile water. Tea dust was ground into a fine powder and extracted at room temperature. The extracted suspension was filtered initially through a coarse filter to remove particulates and subsequently through a micropore filter. The prepared extract was used fresh in the bronchoprovocation and skin testing studies.

Lung function testing was performed before exposure and at 0, 15, 30, and 60 minutes after the cessation of exposure. A positive response (characterizing responders) was defined as a 20 percent fall in FEV₁, or a 25 percent fall in FEF50 or FEF25, or a 50 percent increase in Raw, or a 35 percent decrease in SCaw from the baseline at any measured point following tea allergen challenge. At each measurement, three breaths were performed and the best value was used for the purpose of analysis. Only subjects with a positive response to tea extract were studied. This represented 15 of 25 consecutive healthy volunteers.

Subjects were skin tested with extracts of three different teas (gruzyan, sage, dog rose) using the standard skin prick test. These represent unfermented (green) teas. These are the teas which we observed to have the largest effect on the respiratory system in tea workers. Tea extracts were prepared from tea dust collected in the tea processing industry. The method of Sheldon et al¹⁸ was used for preparing the tea extracts. Skin prick testing with different tea allergens was performed using a dilution 1:500 of the tea extracts (0.02 ml of solution injected). In addition, skin testing was performed with histamine base (1 mg/ml) and a buffer as a control solution. The skin reactions were read after 20 minutes and were considered positive when the wheal was 3 mm greater than the control wheal.

Serum levels of total IgE antibody were measured by PRIST, a direct radioimmunologic sandwich technique based on paper discs as a solid phase.¹⁹ Levels of IgE below 125 kU/L were considered normal.¹⁹

Nonspecific Bronchial Challenge

The same 15 subjects were tested for nonspecific bronchial reactivity by challenge with progressive concentrations of methacholine (3.0, 6.25, 12.5, 25.0, 50.0, 100.0 mg/ml).

Five breaths of each concentration were inhaled. Lung function was measured in a body plethysmograph before and immediately after the inhalation of each concentration of methacholine. The FVC, FEV₁, FEF50, FEF25, Raw, and SCaw were measured.

Statistical Analysis

The mean peak decrements following the various tea provocations were compared to baseline values using the paired Student's *t* test. Differences in peak decrements among the three different teas were compared statistically by an analysis of variance.²⁰

Table 1—Anthropometric Data, Skin Prick Test, IgE, Baseline Lung Function, and PD₅₀FEF₂₅ in 15 Healthy Volunteers

No	Sex	Age, yr	Prick Test*			FVC, Measured		FEV ₁ , Measured		FEF50, Measured		FEF25, Measured		Raw, Measured		SCaw, Measured	
			S	DR	C	IgE, kU/L	% of Normal	L	% of Normal	L/s	% of Normal	L/s	% of Normal	cm H ₂ O/L/s	% of Normal	cm H ₂ O/s	% of Normal
1/F	17	-	-	-	+	<125	84.9	4.20	97.5	4.4	81.5	3.2	110.3	0.16	84.2	1.55	77.2
2/F	23	-	-	-	-	<125	88.6	3.95	106.7	4.3	81.7	2.6	92.9	0.13	68.4	2.19	115.9
3/F	17	-	-	-	-	880	83.4	3.45	84.0	4.2	79.3	2.6	88.1	0.12	66.7	1.89	100.0
4/M	18	-	-	-	-	<125	86.4	4.90	86.9	5.4	95.9	3.2	103.2	0.19	118.8	1.74	106.8
5/M	20	-	-	-	-	<125	107.5	6.00	112.4	7.0	125.0	4.0	129.0	0.09	56.3	1.82	89.2
6/M	21	-	-	-	-	<125	110.1	5.45	117.0	6.8	121.4	3.8	122.6	0.13	72.2	2.22	130.6
7/M	21	-	-	-	-	<125	85.9	5.35	109.2	6.4	113.3	4.0	125.0	0.15	88.2	1.90	85.0
8/M	17	-	-	-	-	<125	94.5	5.30	88.5	4.6	81.1	2.6	81.3	0.10	93.8	2.11	106.0
9/M	17	-	+	-	-	500	90.6	5.50	89.4	5.6	89.1	2.9	93.6	0.10	62.5	2.20	113.9
10/M	17	-	-	-	-	<125	84.7	5.75	88.4	6.0	106.4	3.3	103.1	0.18	105.9	1.78	91.8
11/M	20	-	-	-	-	<125	85.9	4.75	91.1	4.4	78.6	2.1	67.7	0.27	158.8	2.00	97.1
12/M	17	-	+	-	-	>1000	108.9	6.50	101.0	6.2	109.7	2.3	74.2	0.19	105.6	1.31	65.5
13/M	18	-	-	-	-	500	86.6	6.15	84.3	5.0	88.5	2.6	81.3	0.18	105.9	1.70	96.1
14/M	18	-	+	-	-	<125	133.9	7.35	140.4	8.6	154.1	4.4	146.7	0.15	83.3	2.00	97.6
15/M	17	-	+	-	-	145	81.1	4.60	80.0	6.5	114.6	4.0	125.0	0.08	50.0	2.50	130.9
																	100.0

*S, sage; DR, dog rose; C, gruzyan.

MEAN LUNG FUNCTION (FEF₂₅ and S_{Gaw}) CHANGES FOLLOWING BRONCHOPROVOCATION WITH 3 DIFFERENT TEA ALLERGENS IN 10 HEALTHY SUBJECTS

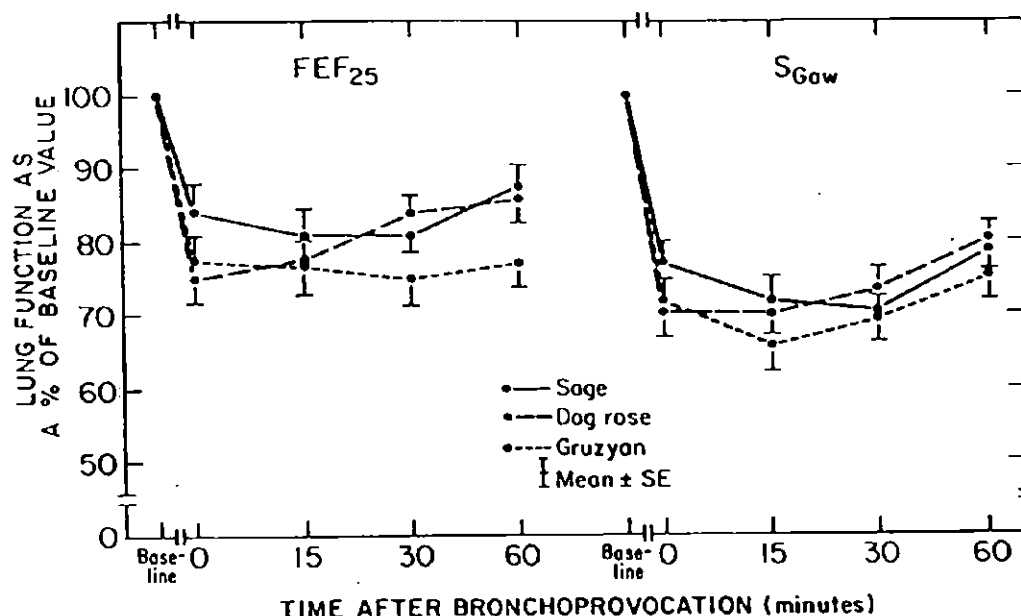


FIGURE 1. Mean relative changes of FEF₂₅ and G_{aw} SE in 15 subjects following bronchoprovocation with three different tea dust extracts.

RESULTS

Table 1 shows anthropometric, immunologic, and baseline lung function data in the 15 healthy subjects tested. Since changes in FEV₁ following methacholine were minimal for this healthy group, nonspecific airway responsiveness was measured by the provocative dose of methacholine required to reduce the FEF₂₅ from baseline (PD₂₀FEF₂₅) by 20 percent. The data for PD₂₀FEF₂₅ are listed in Table 1.

The results of skin prick testing demonstrated that four subjects (26.7 percent) reacted to dog rose and three of them had increased IgE (>1000 kU/L; 500 kU/L; 145 kU/L). One subject (6.7 percent) reacted to gruzyan tea and had a normal IgE value. Two subjects had increased serum IgE levels with negative skin reactions to the tested teas (880 kU/L; 500 kU/L).

The results of the acute effects of different tea allergens on lung function in 15 subjects for FEF₂₅ and S_{Gaw} are presented in Figure 1. In Table 2, the data are analyzed as the maximum decrement over the 60-minute challenge for each individual and expressed as mean $\pm$ SD. There were statistically significant mean acute decreases in all lung function parameters following inhalation of sage, dog rose, and gruzyan tea ($p < 0.001$). The largest mean maximal acute reductions were recorded for S_{Gaw} (sage: -35.6 percent; dog rose: -35.4 percent; gruzyan: -37.4 percent), followed by FEF₂₅ (sage: -26.3 percent; dog rose: -27.7 percent; gruzyan: -25.0 percent), and FEF₅₀ (sage: -19.6 percent; dog rose: -24.1

percent; gruzyan: -25.0 percent) (Table 3). There were no differences in the degree of bronchoconstriction between the three types of tea extracts.

There was no association between the baseline PD₂₀FEF₂₅ and the maximal acute reduction in FEF₂₅ following all three types of tea allergens

Table 2—Lung Function Parameters Before and After Inhalation of Three Tea Extracts (mean $\pm$ SD)

	Sage		Dog Rose		Gruzyan	
	Pre	Post*	Pre	Post	Pre	Post
FVC, L	5.28	4.81	5.31	4.90	5.32	4.85
	+1.06	+0.88	+0.98	+0.97	+0.97	+0.92
p	<0.002		<0.001		<0.001	
FEV ₁ , L	4.53	4.04	4.54	4.00	4.52	3.89
	± 0.72	± 0.59	± 0.67	± 0.67	± 0.73	± 0.53
p	<0.001		<0.001		<0.001	
FEF ₅₀ , L/s	5.83	4.69	5.94	4.51	5.81	4.36
	± 1.08	± 1.04	± 1.26	± 0.86	± 1.20	± 1.14
p	0.003		<0.001		<0.001	
FEF ₂₅ , L/s	3.27	2.41	3.28	2.37	3.37	2.35
	+0.73	+0.62	± 0.69	± 0.70	± 0.75	± 0.82
p	<0.001		<0.001		<0.001	
Raw, cmH ₂ O/L/s	0.14	0.20	0.14	0.19	0.13	0.21
	+0.03	± 0.07	± 0.03	± 0.06	± 0.04	± 0.09
p	<0.001		<0.001		<0.001	
S _{Gaw} , cmH ₂ O/s	2.05	1.32	2.06	1.33	2.11	1.32
	0.40	0.45	0.32	0.42	0.35	0.49
p	<0.001		<0.001		<0.001	

*Post values represent the peak decrement recorded during a 60-minute period.

Table 3—Comparison of Mean ($\pm$ SD) Maximal Decrement in Lung Function Following Inhalation of Various Tea Extracts

	Sage	Dog Rose	Gruzyan
FVC, L	91.33 ± 6.85	91.93 ± 4.46 $p=0.920$	91.13 ± 5.18
FEV ₁ , L	89.67 ± 7.51	88.33 ± 7.49 $p=0.568$	86.67 ± 8.04
FEF50, L/s	81.87 ± 14.85	77.47 ± 14.48 $p=0.632$	76.93 ± 16.74
FEF25, L/s	75.07 ± 15.09	72.93 ± 16.70 $p=0.695$	70.00 ± 16.93
Raw, cmH ₂ O/L/s	143.13 ± 26.67	140.73 ± 30.90 $p=0.409$	154.53 ± 31.76
SGaw, cmH ₂ O/s	65.47 ± 14.89	65.00 ± 13.56 $p=0.702$	61.00 ± 18.79

*Expressed as percent of baseline.

($p>0.05$) using the rank correlation test.

We also examined the relationship between specific sensitivity to tea antigens (*ie*, positive skin tests) or the presence of elevated IgE and the response to inhaled extract. The results are summarized in Table 4. There is no difference between the two subgroups.

DISCUSSION

The potential health hazards of different herbal tea have been described by several authors.^{1,21,22} Grammer and Patterson,³ and Brooks² listed tea as a possible cause of occupational immunologic disease. A case of anaphylactic reaction to camomile tea was described by Benner and Lee.²³

Our data demonstrated that inhalation of sage, dog rose, and gruzyan tea extracts in healthy subjects may cause a significant acute decrease in lung function. These data are comparable to the results obtained in tea workers occupationally exposed to sage, dog rose, and gruzyan tea.⁸ Immunologic studies in tea workers, however, demonstrated higher prevalences of positive skin reactions than in volunteers to extracts such as sage (45 percent), gruzyan (40 percent), mint (35 percent), and dog rose (10 percent).¹¹ Serum levels of total IgE were increased in 27 percent of these tea workers.

In this study, seven out of 15 healthy subjects sensitive to tea inhalation by lung function changes complained of acute symptoms following tea allergen inhalation. Castellan *et al*¹¹ reported that 7 percent of workers in an herbal tea factory complained of a first-day-back to work pattern of chest tightness. This is similar to the findings in our study of tea workers in which 10 percent of the workers reported acute chest

Table 4—Comparison of Largest Change in Lung Function Following Tea Extracts in Subjects With and Without Specific Reactions to Tea Extracts*

Subject	FEV1	FEF50	FEF25	Raw	SGaw	IgE	Skin Test
1	-18	-20	-24	+206	-39		+
3	-19	-33	-31	+155	-34	+	
9	-6	-33	-33	+160	-42	+	+
12	-20	-40	-48	+181	-68	+	+
13	-21	-32	-45	+172	-65	+	
14	-31	-60	-61	+150	-38		+
15	-9	-21	-26	+178	-45	+	+
$\bar{x}$	-18	-34	-38	+172	-48		
SD	± 8.2	± 13.4	± 13.5	± 19.1	± 12.8		
2	-9	-12	-26	+107	-23		
4	-13	-46	-56	+223	-56		
5	-17	-7	-30	+127	-30		
6	-14	-31	-28	+138	-31		
7	-15	-50	-55	+169	-44		
8	-10	-20	-15	+160	-39		
10	-11	-19	-34	+207	-61		
11	-14	-29	-43	+170	-61		
$\bar{x}$	-13	-27	-38	+163	-43		
SD	± 2.7	± 15.3	± 14.4	± 39.1	± 14.9		

*Expressed as percent change from baseline.

tightness more intense at the beginning of the work week or on return to work after a period of absence.⁸ However, the number of workers complaining of this symptom pattern is considerably lower than among textile workers (20 to 40 percent)²⁴ or coffee workers (15 percent).²⁵ The frequency with which our healthy nonexposed volunteers responded to the extract is high (60 percent). It is nonetheless comparable to our experience with challenge with cotton bract extract. Since the exact biochemical nature of the irritant is unknown, it is not possible, at this time, to quantitatively compare occupational and laboratory challenges. Nevertheless, as with CBE, our experience with tea dust extract may lead to useful physiologic and pharmacologic information.²⁶

The mechanism by which the tea dust may act to produce airway obstruction has been postulated to be either nonimmunologic (reflex, inflammatory or pharmacologic) or immunologic (immediate hypersensitivity response). The present study does not allow us to definitively characterize this question, although the fact that nonspecific reactivity in our subjects does not correlate with responsiveness to tea extracts suggests that nonspecific airway irritability may not be an initiating factor in this occupational disease. Experience from our previous study in tea workers suggests that specific skin sensitivity to tea may predict the severity of the airway response.¹² Nevertheless, in the current study among the five subjects with evidence of immediate skin sensitivity (Table 4), no increased airway reactivity was documented. This suggests that pre-existing skin sensitivity to tea extract does not

predict the severity of airway reactivity to this occupational agent.

Lam et al²⁷ suggested that nonspecific bronchial hyperreactivity is likely to be the consequence rather than the predisposing factor in occupational asthma. Our current study suggests this to be the case for airway disease due to tea dust exposure. Further study of this question by routine methacholine inhalation testing during the pre-employment examination of workers entering industries known to give rise to occupational asthma along with regular follow-up examinations may help to answer this question, specifically for tea-related airway disease.

This current study extends our previous observations in tea workers. A large proportion of naive subjects never exposed in the industry to tea dust displays significant degrees of bronchoconstriction following challenge with tea extracts. The degree of nonspecific airway reactivity in these healthy subjects does not appear to influence the severity of this reaction. Similarly, specific reactivity to skin testing with tea extract as well as the measurement of serum IgE does not appear to predict those individuals with more pronounced reactions. These data suggest that in the case of respiratory disease induced by occupational exposure to tea dust, nonspecific airway hyperreactivity as well as specific sensitivity to tea antigens is a result of employment in the industry rather than a risk factor for occupational asthma.

REFERENCES

- 1 Ridkers PM. Toxic effects of herbal tea. *Arch Environ Health* 1987; 42:133-36
- 2 Brooks SM. Occupational asthma. In: Weiss EB, Segal MS, Stein M, eds. *Bronchial asthma*. Boston: Little, Brown and Company, 1985:461-93
- 3 Grammer LC, Patterson R. Occupational immunologic lung disease. *Ann Allergy* 1987; 58:151-59
- 4 Castellani A, Chalmers A. *A manual of tropical medicine*. 3rd ed. New York: William Wood and Co, 1919
- 5 Uragoda CC. Tea-maker's asthma. *Br J Ind Med* 1970; 27:181-82
- 6 Ebihara I. Study on the inhalative allergy of ciliae of leaves: inhalative allergy of the ciliae of tea leaves. *J Sci Labour* 1975; 51:661-65
- 7 Mackay DM. Disease patterns in tea garden in Bangladesh. *J Occup Med* 1977; 19:469-72
- 8 Zuskin E, Skuric Z. Respiratory function in tea workers. *Br J Ind Med* 1984; 41:88-93
- 9 Uragoda CC. Respiratory disease in tea workers in Sri Lanka. *Thorax* 1980; 35:114-17
- 10 Al-Zuhair YS, Cinkolai FF. Ventilatory function in workers exposed to tea and wood dust. *IRCS, Med Sci Microbiol* 1977; 5:190
- 11 Castellani RM, Boehlecke BA, Petersen MR, Thedell TD, Merchant JA. Pulmonary function and symptoms in herbal tea workers. *Chest* 1981; 79:81-85
- 12 Zuskin E, Kanceljak B, Skuric Z, Ivankovic D. Immunological and respiratory changes in tea workers. *Int Arch Occup Environ Health* 1985; 56:57-65
- 13 Zuskin E, Duncan PC, Douglas J. The pharmacological characterization of aqueous extracts of vegetable dusts. *Lung* 1983; 161:301-06
- 14 Commission des Communautés Europeenes, CECA (1971) Aide memoire pour la pratique de l'examen de la fonction ventilatoire per la spiropgraphie. Collection D'Hygiene et de medicine du travail, No. 11, Luxembourg
- 15 Cherniack RM, Raber MB. Normal standards for ventilatory function using an automated wedge spirometer. *Am Rev Respir Dis* 1972; 106:38-46
- 16 Ulmer WT, Reichel G, Nolte D. *Die Lungenfunktion*. Stuttgart: Georg Thieme Verlag, 1976
- 17 Sheldon JM, Lowel RC, Mathews KP. *A manual of clinical allergy*. Philadelphia: WB Saunders Company, 1967:507-31
- 18 Wide L, Porath J. Radioimmunoassay of proteins with the use of Sephadex coupled antibodies. *Biochim Biophys Acta* 1966; 130:257-60
- 19 Johansson SCO. Serum IgND levels in healthy children and adults. *Intern Arch Allergy* 1968; 34:1-4
- 20 Snedecor GW, Cochran WC. *Statistical methods*. ed 6. Ames, IA: Iowa State Press, 1974
- 21 Siegel RH. Herbal intoxication: psychoactive effects from herbal cigarettes, tea, and capsules. *JAMA* 1976; 236:473-76
- 22 Segelman AB, Segelman FP, Karliner J, Sofia RD. Sassafras and herb tea: potential health hazards. *JAMA* 1976; 236:477
- 23 Benner MH, Lee HJ. Anaphylactic reaction to camomile tea. *J Allergy Clin Immunol* 1973; 52:307-08
- 24 Zuskin E, Valic F, Bohuys A. Byssinosis and airway responses due to exposure to textile dust. *Lung* 1976; 154:17-24
- 25 Zuskin E, Valic F, Skuric Z. Respiratory function in coffee workers. *Br J Ind Med* 1979; 36:117-22
- 26 Schachter EN, Buck MC, Zuskin E, Witek TJ, Beck GJ, Tyler D. Airway reactivity and cotton braxet induced bronchial obstruction. *Chest* 1985; 97:51-55
- 27 Lam S, Wong R, Yeung M. Nonspecific bronchial reactivity in occupational asthma. *J Allergy Clin Immunol* 1979; 63:28-34

Maladies respiratoires

Alvéolite allergique

Bibliographie

- * DO PICO, G.A., "Report on Diseases", *American Journal of Industrial Medicine*, vol. 10, pp. 261-265, (1986).
- * JOHNSON, W.M., KLEYN, J.G., "Respiratory Disease in a Mushroom Worker", *Journal of Occupational Medicine*, vol. 23, no. 1, (1981).
- * JONES, A., "Farmer's Lung : An overview and prospectus", *Ann. Am. Conf. Gov. Ind. Hyg.*, vol. 2, pp. 171-182, (1982).
- LARRY, A., "Hypersensitivity Pneumonitis", Zenz C., chap. 15, *Occupational Medicine*, chap. 15, 2nd Ed., (1988).
- * LOPEZ, M., SALVAGGIO, J.E., "Epidemiology of Hypersensitivity Pneumonitis/Allergic Alveolitis", *Monogr. Allergy*, vol 21, pp. 70-86, (1987).
- * SAUVAGET, J., AERTS, J. et al., "Manifestations respiratoires avec présence de précipitines au charençon de blé, *Archives des maladies professionnelles, de médecine du travail et de Sécurité Sociale*, vol. 39, no. 10-11, p. 617-623, (1978).
- * THONY, G., *Maladie des poumons des fermiers*, CLSC Jardin du Québec, non daté.

* Articles inclus

Report on Diseases

Rapporteur: Guillermo A. doPico, MD

Specific diseases associated with the agricultural environment were identified as allergic rhinitis and asthma, pneumonitis/alveolitis, the organic dust toxic syndrome and bronchitis. Diagnostic criteria were formulated and current research techniques, in terms of epidemiological studies were outlined. The workgroup summarized a priority for epidemiological studies to evaluate the incidence of the different diseases as well as the identification of predisposing host and environmental factors.

Key words: diagnostic criteria, organic dust syndrome, allergic rhinitis and asthma, pneumonitis/alveolitis, bronchitis, epidemiology

INTRODUCTION

Exposure to organic dusts found in agriculture may result in various symptoms and disease conditions. Some research has investigated the impact of the environment on the health of farm workers, but there are still significant gaps in our knowledge. In this report, we first identify specific diseases associated with the agricultural environment and then make several recommendations for increasing our knowledge of these disease conditions, especially in surveillance of farmers' health.

DISEASES ASSOCIATED WITH THE AGRICULTURAL ENVIRONMENT

Knowledge of the direct relationship between agents in the agricultural environment and specific diseases is still limited. Certain diseases are, however, specifically related to farming. Four such diseases will be discussed here: allergic rhinitis and asthma, pneumonitis/alveolitis, organic dust toxic syndrome, and bronchitis.

For the purpose of this report, we define atopic predisposition as a constitutional tendency for an individual to mount an IgE response of mucus membranes to low doses of common allergens. A commonly used method of assessing this condition is by one or more positive skin-prick test reactions to common environmental allergens.

Allergic Rhinitis and Asthma

It is reasonable to assume that there is a greater allergenic load to specific allergens in farmers than in urban populations. However, a "healthy worker effect"

Department of Medicine, H6/328 Clinical Science Center, Madison, WI
Address reprint requests to Guillermo A. doPico, Department of Medicine, H6/328 Clinical Science Center, 600 Highland Avenue, Madison, WI 53792.
Accepted for publication January 16, 1986.

should be taken into consideration when interpreting prevalence data. The prevalence of sensitization to farm aeroallergens and of rhinitis and asthma induced by these aeroallergens in farmers has not been shown to differ from that in nonfarmers, but information is limited. Sensitization to certain allergens, specific for the farm environment, eg, storage mites and certain grains (oats, barley), could be more prevalent in farmers. In Finland, sensitization to animal epithelia, other than those from cats and dogs, was more common among dairy farmers than among teachers living in a city. However, sensitization to molds commonly found on farms was less prevalent among farmers than among teachers.

Atopic individuals with respiratory symptoms are at a higher risk of aggravating their disease in the farm environment or during farm work. Atopic predisposition as such, however, is not known to increase the risk of developing disease among farmers. There is some evidence of an association between atopic predisposition (determined by skin-prick test) and chronic bronchitis. That relationship may play a pathogenic role in the airways dysfunction found in grain handlers.

Pneumonitis/Alveolitis

Hypersensitivity pneumonitis (HP, or extrinsic allergic alveolitis) in agricultural workers (often referred to as farmer's lung) can be induced by interaction between cells in the lung parenchyma and inhaled materials via specific and nonspecific immunological mechanisms. The risk of developing chronic interstitial disease (fibrosis) increases markedly after five or more symptomatic recurrences.

The main criteria for diagnosis are 1) exposure to offending antigens revealed by history and aerobiological or microbiological investigations of the environment; measurements of antigen-specific IgG antibodies (eg, serum precipitin test) may give additional evidence for exposure; 2) symptoms compatible with HP appearing or worsening some hours after antigen exposure; 3) lung infiltrations compatible with HP visible on chest radiographs.

Additional criteria are 1) basal crepitant râles audible on auscultation of the lungs, 2) impairment of the pulmonary diffusing capacity, 3) arterial oxygen tension (or saturation) either decreased at rest or normal at rest but decreased during exercise, 4) restrictive ventilatory defect in the spirometry, 5) histological changes compatible with HP in a lung biopsy specimen, 6) positive provocation test either by work exposure or by controlled inhalation challenge.

The workgroup agreed that the diagnosis can be considered confirmed if, after adequate procedures for differential diagnosis have been applied to exclude other diseases with similar symptoms and clinical findings, the patient fulfills all the main criteria and at least two of the additional criteria. If the criteria are otherwise fulfilled, but the chest radiograph is normal, the diagnosis can be considered confirmed if a lung biopsy has been made and the specimen shows changes compatible with HP. Bronchoalveolar lavage (BAL) fluid showing predominantly increase in lymphocytes and macrophages gives additional support to the diagnosis. Lung biopsy, BAL, or provocation tests are not routine diagnostic procedures for HP. They should be restricted to such cases where diagnostic criteria of HP are not otherwise fulfilled and a confirmed diagnosis is required for compensation purposes.

The prevalence of clinically recognized HP among agricultural workers appears to be relatively low. The reported prevalence of HP to moldy hay, fodder and grain, or moldy shredding and threshing dusts varies between 57 and 86 per 1,000 farmers,

but it is most likely about two to seven per 1,000 European or American farmers. However, in spite of the relatively low prevalence, it is an important disease to diagnose, because if it goes unrecognized or if several symptomatic episodes occur before its recognition, chronic irreversible disease with disabling symptoms may develop. The prevalence of minor or clinically unrecognized cases of the disease may be significant, but criteria and methods to detect these cases have not been developed.

The causative agent in HP is related to the type of agricultural operation. Among dairy farmers, *Micropolyspora* or *Thermoactinomyces* species are the main causative agents. There is strong evidence, however, suggesting that other agents can be involved. Avian proteins are etiologic agents of HP in chicken and turkey farmers; *T. sacchari* is the agent in bagasse workers, *Penicillium frequentans* in cork workers; *P. casei* in cheese washers; and *Cryptostoma corticale*, *Alternaria* spp, *Rhizopus* spp, *Aspergillus clavatus*, *Graphium* spp, and *Aureobasidium* spp in wood workers. The role of the ubiquitous *A. fumigatus* remains controversial. We suspect, however, that there are many unrecognized etiological agents of HP still to be identified among agricultural workers.

The prevalence of HP related to exposure to avian proteins among chicken and turkey farmers is low if the above diagnostic criteria are applied. In the German Democratic Republic, two cases were recognized among 339 poultry farmers. No cases have been recognized in Finland, and in France an estimated four cases per year occur.

Antibodies to the above agents present in the farm environment reflect exposure but are not related to the pathogenesis of the disease. The detection of antibodies can, however, be a valuable biological monitor of cumulative exposure. Their absence, however, does not exclude the presence of HP or negate specific exposures to yet unknown etiologic agents.

Organic Dust Toxic Syndrome

Exposures to high concentrations of organic dust during agricultural work or handling of agricultural products may result in influenza like syndrome with or without respiratory symptoms and usually without clinical or radiological evidence of HP. However, there is evidence that a subclinical alveolitis can be present. Leukocytosis and fever are almost invariably present. Potential etiological agents are dusts containing mold and bacteria, endotoxins, or other unidentified agents. Although prevalence rates may reach 30-40% of the exposed, not all workers exposed develop the symptoms. The severity of the response varies among individuals exposed to the same environment.

The toxic syndrome has been associated with exposure to moldy agricultural materials and has formerly been referred to as "pulmonary mycotoxicosis." Mycotoxin, however, has not been found to be associated with the febrile syndrome found in Wisconsin or New York farmers. Serum antibodies to fungi or bacteria present in the moldy materials are seldom detected.

In several case studies, bronchoalveolar lavage fluid (BAL) revealed increased numbers of polymorphonuclear cells and macrophages and evidence of alveolitis. Biopsy material indicated that an acute inflammatory reaction (alveolitis) was present.

Several varieties of this toxic syndrome have been described, although they probably all comprise descriptions of the same disease, precipitated in different environments. Farmers exposed to moldy silage, moldy grain, moldy wood chips,

etc, develop a syndrome characterized by a flu-like illness 4-6 hr after a massive exposure. In those exposed to moldy silage, the peak incidence occurs during late summer months and fall, whereas symptoms of HP tend to occur during the winter months as in farmer's lung disease. Grain fever is a flulike illness with or without airway obstruction developing during or after exposure to high levels of grain dust. Some workers develop symptoms only upon exposure to grain dust after prolonged periods of nonexposure but not on recurrent exposures, suggesting the development of tolerance. Pig or fowl fever is uncommon but recognized after intense exposure to these animals while weighing or transporting.

Overall, the organic dust toxic syndrome appears to be self-limiting and does not appear to result in permanent physiological derangements or progressive disease. This, however, needs to be confirmed by longitudinal studies, since progression into HP or chronic bronchitis could occur in some instances. Grain dust and swine and fowl dust have been found to be contaminated with bacterial endotoxins, but the association between the febrile syndrome and the concentration of endotoxin has not been studied in detail.

Evidence showing that the organic dust toxic syndrome is distinct from HP is as follows. 1) A considerable proportion of individuals experiencing an exposure become symptomatic. 2) Exposure levels are nearly uniformly quite high. 3) There is no evidence of progressive lung disease despite repeated exposures. 4) Serum antibodies are not detected in the majority of patients. 5) Alveolar lavage studies done during the acute phase reveal a predominance of neutrophils rather than lymphocytes. 6) Biopsy of acute cases shows acute inflammation without granulomas.

Bronchitis

Evidence from a variety of sources suggests that inhalation of agricultural dusts is associated with an increased prevalence of chronic bronchitis (defined as cough and sputum for 2 years or more) with or without airway obstruction. The prevalence of chronic bronchitis in farmers is largely unknown. A study involving 80% of the working males in a Swiss village found a tenfold increase in symptoms and three- to tenfold increase in dyspnea and airway obstruction in farmers vs nonfarmers matched for age and smoking. Data from studies in Vermont, Ontario, and Finland also support the conclusion that chronic bronchitis is a significant problem in the farm environment.

Epidemiological studies have shown a high prevalence of respiratory disorders among handlers of grain other than farmers. In grain elevator operators, for example, grain dust not only causes cough, expectoration, wheezing, and chest tightness but observable reductions in airway function, which are at least partially reversible after cessation of exposure. The effect of grain dust is of similar magnitude to the effect of smoking, and these two factors act in an additive fashion. Dust from swine and poultry confinement buildings has been found to result in an increased rate of reported cough and sputum though controlled studies demonstrating meaningful reductions in pulmonary function are lacking.

The workgroup recognized the problems related to epidemiological studies, such as use of questionnaires, confounding effects of smoking, self-selection of workers leaving the work force because of symptoms, and estimation of exposure intensity in studies on chronic bronchitis. The relevance of the reported symptoms and of the measured losses of lung function in terms of eventual development of

dyspnea and disability is not currently clear. Nevertheless, there remains a clear perception that chronic bronchitis is a real problem in the farm environment.

CURRENT RESEARCH TECHNIQUES

Surveillance

Medical surveillance programs should be an organized attempt to detect disease early and prevent chronic disabling symptoms by protecting the host and modifying the environment rather than a mere collection of information. Furthermore, data collected during medical surveillance should be regularly analyzed for trends, which could lead to recognition of new diseases related to farming and/or detection of health deterioration trends not recognizable in the individuals' data.

Epidemiological Studies

It is highly recommended that epidemiological research and surveillance programs use acceptable, standardized techniques whenever feasible. Guidelines and standards for use of questionnaires and pulmonary function tests have been proposed by the World Health Organization in Europe and the American Thoracic Society (ATS) in the U.S.

AREAS OF RESEARCH

There is a need for more epidemiological studies on the prevalence of sensitization and of allergic disease induced by inhalation of aeroallergens in the farming population compared to rural and urban nonfarming populations. The differences in exposure in various types of farming need to be defined from quantitative and qualitative points of view. The possibility of identifying factors having predictive value for eventual development of serious allergic problems should be explored.

The prevalence of asthma and/or acute bronchitis with assessment of the relative contribution of smoking should be determined by well designed cross-sectional epidemiological studies. The long-term effects and significance of the clinical, physiological, and immunological manifestations should be assessed by longitudinal studies. Detection of predisposing host and environmental factors, eg, atopic status and bronchial hyperreactivity, should be an important aim of all studies. Of great significance will be studies on the relationships between identifiable and measurable exposures and clinical, physiological, and immunological manifestations of disease. Animal and human research in the etiology and pathogenesis of the common pulmonary reactions to organic dust should lead to prevention of disabling disease.

Respiratory Disease in a Mushroom Worker

William M. Johnson, M.D., M.P.H., M.I.H., and John G. Kleyn, Ph.D., M.S.P.H.

A patient with allergic alveolitis demonstrated by lung biopsy is described in a mushroom worker in Washington State presenting with severe airways obstruction. This is the first case of mushroom worker's lung reported in the United States outside the mushroom industry in Pennsylvania. The processes of commercial mushroom growing are discussed, and the literature on mushroom worker's lung is reviewed.

Respiratory disease among mushroom workers was first reported in 1959, when Bringham et al¹ reviewed sixteen cases of febrile illness among Puerto Rican migratory workers in Pennsylvania. Sakula² in 1967 first used the name mushroom worker's lung in describing four cases in England which resembled farmer's lung. In 1970 two cases of allergic alveolitis were described among mushroom workers in England and two cases were reported from eastern Canada.^{3,4} In 1972 Chan-Yeung et al⁵ reported a case from British Columbia, Canada, and in 1974 Stewart⁶ reported six cases from England. Lockey⁷ reviewed the commercial growing of mushrooms and reported symptoms of an unspecified number of mushroom workers in Pennsylvania. Stolz et al⁸ in 1976 reported that the chest roentgenograms of eight of 26 symptomatic mushroom workers in Pennsylvania were positive for allergic alveolitis.

The present report describes the first case of mushroom worker's lung reported in the United States outside the mushroom industry in Pennsylvania and is the second case of allergic alveolitis in a mushroom worker confirmed by lung biopsy. The presentation with severe airways obstruction is atypical.

Case

The patient is a 39-year-old Puerto Rican male who

had been employed since 1970 at a mushroom farm in Washington State in a variety of duties including spawning. In November 1976 he was admitted to another hospital with symptoms of progressive shortness of breath, anterior chest pain, a dry cough, frontal headaches, a 23-pound weight loss, myalgias, and generalized malaise of four months' duration. In the absence of any previous pulmonary symptoms, he discontinued smoking between one and two packs of cigarettes a day, an amount he had smoked since age 15. He had no history of allergies nor hay fever; however, he had a brother with the onset of asthma in his twenties. Admitting arterial blood gases during that hospitalization were P_{O_2} , 39 mmHg, P_{CO_2} , 52 mmHg; and pH, 7.36. The serum alpha-1 antitrypsin level was 360 mg/100ml (normal 210 to 500). Spirometry showed a forced expiratory volume in one second (FEV_{1.0}) of 0.76 liters, a forced vital capacity (FVC) of 1.91 liters, and a FEV_{1.0}/FVC ratio of 0.41. A chest roentgenogram was interpreted as suggestive of bilateral diffuse micronodular changes in the lower lung fields. He was discharged with the diagnosis of chronic obstructive pulmonary disease.

He was referred to a specialist in pulmonary diseases who started prednisone 20 mg twice a day, which was eventually reduced to a dosage of 5 to 10 mg daily. He was advised to avoid further exposure to mushroom compost, but continued working on the mushroom farm in jobs which did not involve entering the mushroom houses. He continued to have the previously mentioned symptoms in addition to recurrent chills. He was referred to the Chest Clinic at Harborview Medical Center, where he was admitted in December 1977. He was very dyspneic and his temperature was 37.0°C. Auscultation of the chest revealed bilateral inspiratory crackles. There was no cyanosis, clubbing nor edema.

A chest roentgenogram showed increased interstitial markings. The hematocrit was 58%, the hemoglobin was 19.8 g/100 ml, the leucocyte count was 6,700/cu mm, and the absolute eosinophil count was 438/cu mm. The serum alpha-1 antitrypsin level was 355 mg/100 ml. An intermediate strength tuberculin skin test was positive at 48 hours

From the Departments of Environmental Health and Medicine, University of Washington, Seattle, WA 98195. Dr. Johnson's current address is: Pulmonary Disease Service, P.O. Box 481, Eisenhower Army Medical Center, Fort Gordon, GA 30905, and Dr. Kleyn is a Private Consultant, 3013 36th Avenue, S.W., Seattle, WA 98126.

with 20 mm induration. Three sputum cultures were negative for *Mycobacterium tuberculosis*. Arterial blood gases on room air were P_{O_2} , 47 mmHg, P_{CO_2} , 46 mmHg, and pH 7.40. Pulmonary function studies obtained two weeks prior to admission included vital capacity (VC), 3.36 liters (82% of predicted); $FEV_{1.0}$, 1.04 liters (30% of predicted); $FEV_{1.0}/VC$, 0.31; total lung capacity, 6.65 liters (110% of predicted); residual volume, 3.29 liters (188% of predicted); single breath diffusing capacity (DL_{CO}), 29.9 ml/min/mmHg (113% of predicted); and DL_{CO} /lung gas volume, 4.5 (102% of predicted). The $FEV_{1.0}$ increased 27% after a bronchodilator aerosol.

Following treatment with intravenous aminophylline, an open lung biopsy of the lingula was performed. Histologic examination showed focal nodular infiltration of lymphocytes and plasma cells admixed with a few eosinophils in the interstitium and around the bronchioles. In addition, there were focal aggregates of epithelioid histiocytes and giant cells. The biopsy was interpreted as consistent with acute and chronic stages of allergic alveolitis. Fungal cultures of the lung biopsy tissue were negative.

Agar gel double diffusion studies were done to detect serum precipitins according to a microscopic slide method.⁹ The following results were obtained: strong positive (3+), extract of phase 2 compost; positive (2+), extract of spent compost, *Thermoactinomyces vulgaris*; and weak positive (1+), *Micropolyspora faeni*, *Bacillus licheniformis*, *Aspergillus fumigatus*, *Humicola grisea* var. *thermoidea*.

The patient was discharged on prednisone 60 mg daily with a marked improvement in respiratory symptoms. He did not return to work at the mushroom farm. More than two years following the open lung biopsy his symptoms included dyspnea on exertion and occasional nocturnal wheezing. Airways obstruction persisted with $FEV_{1.0}$ values averaging 1.5 liters with some improvement after bronchodilator aerosol; medications included prednisone 10 mg every other day, beclomethasone dipropionate inhaler, metaproterenol inhaler, oral aminophylline, and terbutaline.

Discussion

Some knowledge of the processes of commercial mushroom growing is necessary for an understanding of the risks of lung disease associated with this occupational environment. The historical and technical aspects of commercial mushroom growing have been reviewed by Atkins.¹⁰ Table 1 lists the major activities in commercial mushroom growing.

At the previously cited mushroom farm in Washington State wheat straw and, to a lesser extent, rye grass straw are mixed with horse manure, cottonseed, and gypsum. Chicken manure has also been used. The compost is prepared outdoors in piles, and spontaneous heat generation takes place sufficiently to achieve a temperature of 160°F in the interior of the piles. This is called phase 1 composting.

Commercial mushrooms are grown in either stationary beds or portable tray mushroom houses. Both types of operations are used at this mushroom farm, whose windowless houses are built with cedar wood. In portable tray operations, filling of trays with compost, addition of

Table 1. — Activities in Commercial Mushroom Growing.

1. Composting, outdoors (phase 1)
2. Filling shelves or trays with compost
3. Composting, indoors (phase 2)
4. Spawning
5. Casing
6. Picking
7. Sterilizing spent compost
8. Dumping spent compost

mushroom spawn, and dumping of spent compost are performed in a building apart from the growing houses. In contrast, in stationary bed operations all of the above operations are conducted inside the growing houses, where tiered wooden beds are filled with compost manually removed from a conveyor belt placed down a narrow central walkway. In stationary bed operations, phase 2 composting takes place inside the growing houses, where a compost temperature of 140°F is maintained for approximately eight to ten days followed by cooling to 74°F for a few days. Spawning is then performed manually with the introduction of mushroom mycelium into the compost. After the spawn has grown for about two weeks, the compost is covered with a thin layer of sphagnum peat as a casing material.

The mushrooms grow in about five or six flushes or crops which are picked periodically over a period of about six weeks, until the nutrient value of the compost is exhausted or spent. The spent compost is steamed for four hours at 150°F. A conveyor belt is placed down the central walkway of a stationary bed house, and the workers transfer the spent compost with pitchforks to the conveyor belt which carries it to a dump truck.

Mushroom worker's lung is considered a form of extrinsic allergic alveolitis due to a hypersensitivity reaction to inhaled organic antigens. The conditions of commercial mushroom growing under which compost is heated at high temperature and humidity provide an ideal environment for the growth of thermotolerant fungi and thermophilic actinomycetes. *Micropolyspora faeni* and *Thermoactinomyces vulgaris* are thermophilic actinomycetes found in moldy hay, are mentioned as the antigens responsible for farmer's lung, and are frequently mentioned as associated with mushroom worker's lung.¹¹⁻¹⁴ Other microbial antigens possibly associated with mushroom worker's lung have been mentioned in reports by Lockey,⁷ Schulz et al.,¹⁵ and Stewart and Pickering.¹⁶ The microflora of composts during phase 1 and phase 2 composting have been reviewed by Lacey,¹⁷ and the microflora of spent compost have been studied.

The exact antigens responsible for mushroom worker's lung are not known. Precipitin studies were not performed in a total of 42 cases reported in the two largest series.^{1, 8} Precipitins were positive to extracts of compost obtained after spawning in two reported cases and before spawning in three reported cases.^{1, 8} Precipitin reactions were positive to mushroom spores in two cases reported by Stewart.⁸ Sakula reported one case with precipitins positive for *Thermoactinomyces vulgaris* and one case with precipitins positive for *Micropolyspora faeni*.³ The presence of serum-precipitating antibodies is of limited

etiological significance, because such antibodies are common in asymptomatic individuals exposed to organic antigens.¹⁴

Six of eight published articles about mushroom worker's lung report cases in association with mushroom spawning.^{2-4,6} In contrast, Bringham et al¹ reported 14 of 16 patients became ill while laying down fresh compost beds. Lockey⁵ reported illness limited to workers who dumped spent compost from which mushrooms had been harvested.

Pulmonary function tests in extrinsic allergic alveolitis usually demonstrate a restrictive pattern with a reduction in vital capacity, compliance, and diffusing capacity accompanied by little or no airways obstruction.¹¹⁻¹⁴ Hypoxemia may be severe. Pulmonary function usually is reversible in the acute form of the disease with return to normal following treatment with corticosteroids, or simply cessation of exposure, although abnormal pulmonary function may persist.¹⁴

Restrictive dysfunction may progress with or without continuing exposure,¹¹⁻¹⁴ and airways obstruction may be prominent in some patients with chronic allergic alveolitis.¹⁹⁻²⁴ The chronic form of allergic alveolitis, as seen in this patient, may present in a less common manner with a bronchospastic syndrome suggesting chronic obstructive pulmonary disease or chronic asthma.²⁵ Inhalation challenge studies in bird fanciers with allergic alveolitis have demonstrated both immediate obstructive responses before the typical delayed restrictive response and delayed obstructive responses.²⁶⁻²⁷ A Type 3 allergic mechanism, which is thought to play an important role in the pathogenesis of allergic alveolitis,²⁸ also might be important in the development of airways obstruction in patients with allergic alveolitis.²⁴

The patient described in this report with a family history of a brother with asthma may have had an asthmatic predisposition. It is unlikely that cigarette smoking could account for the severe degree of airways obstruction in this 39-year-old male with no prior history of respiratory difficulties and a normal alpha-1 antitrypsin level. Corticosteroid therapy may have suppressed his symptoms sufficiently to permit his return to work with continuing exposure to the responsible antigen(s). It is interesting that this patient presented with systemic symptoms compatible with allergic alveolitis with no symptoms of wheezing. Allergic alveolitis was demonstrated by lung biopsy.

A medical surveillance program did not exist at this mushroom farm. Many of the workers were immigrants from southeast Asia, Puerto Rico and Mexico, who spoke English poorly or in a limited manner. The most important measure in the treatment of a mushroom worker with respiratory or systemic symptoms of allergic alveolitis, or both, is complete avoidance of the offending antigen(s) in order to prevent progressive morbidity. This usually means leaving the mushroom farm for another occupation; this measure would pose an immediate economic threat to the typical, low-income mushroom worker in the northwestern United States.

The authors wish to thank Leonard D. Hudson, M.D., and Theodore F. Wezler, Ph.D., for their review and comments.

References

1. Bringham LS, Byrne RN, and Gershon-Cohen J: Respiratory disease of mushroom workers. *JAMA* 171:15-18, 1959.
2. Sakula A: Mushroom-Worker's lung. *Br Med J* 3:708-710, 1967.
3. Jackson E and Welch KMA: Mushroom worker's lung. *Thorax* 25:25-30, 1970.
4. Craig DB and Donevan RE: Mushroom-Worker's lung. *Can Med Assoc J* 102:1289-1293, 1970.
5. Chan-Yeung M, Grzybowski S, and Schonell ME: Mushroom worker's lung. *Am Rev Respir Dis* 105:819-822, 1972.
6. Stewart CJ: Mushroom worker's lung — Two outbreaks. *Thorax* 29:252-257, 1974.
7. Lockey SD: Mushroom workers' pneumonitis. *Ann Allergy* 33:282-288, 1974.
8. Stolz JL, Arger Ph, and Benson JM: Mushroom worker's lung disease. *Radiology* 119:61-63, 1976.
9. Crowle AJ: A simplified micro double-diffusion agar precipitin technique. *J Lab Clin Med* 52:784-787, 1958.
10. Atkins FC: *Mushroom Growing Today*. London: Faber and Faber, 1961.
11. Parkes WR: *Occupational Lung Disorders*. London: Butterworths, 1974, p 394.
12. Morgan WKC and Seaton A: *Occupational Lung Diseases*. Philadelphia: W. B. Saunders, 1975, pp 289-320.
13. Fink JM: Hypersensitivity Pneumonitis in Allergy: Principles and Practice. E. Middleton, C. E. Reed, and E. F. Ellis (Eds.). St. Louis: C. V. Mosby, 1978, pp 855-867.
14. Pepys J: Pulmonary Aspergillosis. Farmer's Lung and Related Diseases in Immunological Diseases (3rd Edition). M. Samter (Ed.). Boston: Little, Brown, 1978, pp 692-717.
15. Schultz KH, Felten G, and Hausen BM: Allergy to the spores of *pleurotus florida* (Letter). *Lancet* 1:29, 1974.
16. Stewart CJ and Pickering CAC: Mushroom Worker's Lung (Letter). *Lancet* 1:317, 1974.
17. Lacey J: Actinomycetes in Soils, Composts, and Fodders in The Actinomycetales, G. Sykes and F. A. Skinner (Eds.). London: Academic Press, 1973, pp 231-251.
18. Fink JN, Schlueter DP, Sosman AJ, et al: Clinical Survey of Pigeon Breeders. *Chest* 62:277-281, 1972.
19. Barbee RA, Callies Q, Dickie HA, and Rankin J: The long-term prognosis of farmer's lung. *Am Rev Respir Dis* 97:223-231, 1968.
20. Allen DH, Williams CV, and Woolcock AJ: Bird breeder's hypersensitivity pneumonitis: Progress studies of lung function after cessation of exposure to the provoking antigen. *Am Rev Respir Dis* 114:555-566, 1976.
21. Hapke EJ, Seal RME, and Thomas CO: Farmer's lung. A clinical, radiographic, functional, and serological correlation of acute and chronic stages. *Thorax* 23:451-468, 1968.
22. Schlueter DP, Fink JN, and Sosman J: Pulmonary function in pigeon breeders' disease. *Ann Intern Med* 70:457-470, 1969.
23. Seal RME: Pathology of Extrinsic Allergic Broncho-Alveolitis, in Alveolar Interstitium of the Lung. Pathological and Physiological Aspects. Progress in Respiration Research. Vol. 8. Basel: S. Karger, 1975, pp 66-73.
24. Schatz M, Patterson R, and Fink J: Immunologic lung disease. *N Engl J Med* 300:1310-1320, 1979.
25. Molina C: Broncho-Pulmonary Immunopathology. Edinburgh: L. Churchill Livingstone, 1976, pp 60-126.
26. Hargreave FE and Pepys J: Allergic respiratory reactions in bird fanciers provoked by allergen inhalation provocation tests. *J Allergy Clin Immunol* 50:157-173, 1972.
27. Pepys J: Nonimmediate Asthmatic Reactions in Bronchial Asthma: Mechanisms and Therapeutics. E. B. Weiss and M. S. Segal (Eds.). Boston: Little, Brown, 1976, pp 231-256.
28. Roberts RC and Moore VL: Immunopathogenesis of hypersensitivity pneumonitis. *Am Rev Respir Dis* 116:1075-1090, 1977.

Dr. Arden Jones received his bachelor of technology and PhD degrees from The University of Bradford in England. He is primarily a microbiologist by training. He has been in a postdoctoral fellowship program for the past eighteen months at the Marshfield Medical Foundation in Marshfield, Wisconsin, studying the microbiology and antigens of organisms implicated in hypersensitivity pneumonitis and like diseases. For the past 20 years, Marshfield Clinic has been a leader in the United States in the study of that particular disease entity or group of diseases.

Farmer's lung: an overview and prospectus[†]

Introduction

The dusts that emanate from agricultural produce have been recognized and documented as respiratory hazards for several centuries.⁽¹⁾ Farmer's lung disease was described and named as a distinct entity only 50 years ago,⁽²⁾ and in the last 25 years, intensive study of this disorder has revealed many characteristics of its etiology, natural history, and epidemiology. However, questions concerning the immunopathogenesis, diagnosis, methods of management and prevention, and the predisposing factors still require resolution.

Farmer's lung belongs to a group of allergic disorders known generically as the hypersensitivity pneumonitides, or in Britain as the extrinsic allergic alveolitis. These disorders show a common symptomatology and pathology, but are distinct from other allergic respiratory diseases, such as bronchial asthma and rhinitis, both clinically and in the section of the population affected. Hypersensitivity pneumonitis develops in the peripheral tissues of the lung as a result of a repeated exposure to organic dusts of a fine particulate nature. It occurs in only a small undefined group of the exposed population. In contrast, asthma and rhinitis are responses to the deposition of allergens in the bronchial tree and upper respiratory tract. These reactions affect the 10% of the population defined as atopic, i.e., individuals with hyperreactive airways or high levels of circulating reaginic (IgE) antibodies.

There now exists an impressive list of hypersensitivity pneumonitides due to airborne organic dusts from a wide variety of sources, some of which are listed in Table I. Farmer's lung is the archetypal example of these disorders, being the result of exposure to dusts from mouldy hay,

grain, and other feed crops. More specifically, the antigenic agents are the spores and products of the thermophilic actinomycetes, *Micropolyspora faeni*, *Saccharomonospora viridis*, and *Thermoactinomyces* species (spp.). Hypersensitivity pneumonitis can occur under a wide variety of occupational or recreational settings resulting in dust or antigen exposure. Many of these disorders are the response to microbial antigens. However, many organic dusts of suitable particle size can induce this disease. Furthermore, certain highly reactive organic chemicals which are not antigenic in their own right, may haptenize with proteins in the lung to provide the antigenic insult for disease development, e.g., toluene diisocyanate⁽³⁾ and trimellitic anhydride.⁽⁴⁾

Etiology

Factors which favor the extensive proliferation of the microorganisms which cause farmer's lung have been determined by studying naturally occurring and experimentally produced mouldy hays.⁽⁵⁻⁷⁾ The circumstances which predisposed towards the simulated production of farmer's lung hays were the high initial moisture content at baling, and the high temperatures subsequently generated in the bale. Hays baled with a moisture content of over approximately 30%, heat spontaneously, initially as a result of enzymatic activity of the plant materials, but predominantly as a result of the metabolic respiration of the saprophytic microflora. As the conditions of pH, temperature,

[†] This work was supported in part by Grant HL-15389 from the Wisconsin Pulmonary Specialized Center for Research and by the Marshfield Medical Foundation, Inc.

TABLE I
Hypersensitivity Pneumonitides/Extrinsic Allergic Alveolitis Due to Organic Dusts

Disease/Occupation	Material	Specific Antigens
Farmer's lung	Mouldy hay/grain	<i>Micropolyspora faeni</i> <i>Thermoactinomyces</i> spp. <i>Saccharomonospora viridis</i>
Bird breeders	Bird droppings/dander	Avian proteins
Mushroom workers	(i) mushroom compost (ii) mushroom spores	Actinomycetes? <i>Pleurotus florida</i>
Malt Workers	Mouldy sprouting barley	<i>Aspergillus clavatus</i> <i>Aspergillus fumigatus</i>
Paper mill workers	Mouldy maple logs Mouldy logs	<i>Cryptosporium corticale</i> <i>Alternaria</i> sp. <i>Rhizopus</i> sp. <i>Aspergillus fumigatus</i>
Humidifier fever	Contaminated humidifiers	<i>Thermoactinomyces</i> spp. protozoae (<i>Naegleria</i> sp.)
Cheese washers	Mouldy cheeses	<i>Penicillium casei</i>
Paprika splitters	Mouldy paprikas	<i>Mucor stolonifer</i>
Suberosis	Mouldy cork	<i>Penicillium frequentans</i>
Bagassosis	Mouldy Sugar cane fibre	<i>Thermoactinomyces sacchari</i>
Sequoiosis	Mouldy Wood dust	<i>Aureobasidium</i> sp. <i>Graphium</i> sp.
Sauna takers	Contaminated water	<i>Aureobasidium</i> sp.
Sewage workers	Sewage dust	?
Pituitary snuff takers	Pituitary snuff	Pituitary proteins

oxygen, and nutrient availability change within the bale, a succession of fungal, bacterial, and actinomycete populations rise and fall, culminating in a climax community of thermophilic actinomycetes. These organisms proliferate rapidly between the temperatures of 40 to 60°C producing a mycelial network and spores in the manner of the fungi. As moisture is driven off by the elevated temperatures and metabolites build to inhibitory concentrations, the hay cools and the massive microbial proliferation slows. The resulting bale is discolored, dry, friable, and extremely dusty. This process may be complete within one or two weeks.

In the winter months when such hays are used for feed or bedding in the confines of the barn or cowshed, the farmer breaks open the bale to release dense clouds of dust. On microscopic examination and microbiological culture, this dust is seen to be composed principally of the

spores of the thermophilic actinomycetes.^(8,9) In such situations, concentrations of up to 1.6×10^9 spores/m³ have been measured; a man doing light work in this environment has been estimated to retain 7.5×10^5 spores/minute in his lungs.⁽¹⁰⁾

Grain and other forage crops, when stored improperly in bins or silos, will also undergo self-heating, and, when shifted, release the clouds of microbial spores which cause farmer's lung.⁽¹¹⁾

Of the many microorganisms found in farmer's lung dusts, the spores of *M. faeni*⁽¹²⁾ are usually the most abundant and are the principal cause of the disease in Britain⁽¹³⁾ and Wisconsin.⁽¹⁴⁾ At 55°C on laboratory media, it grows as small raised orange-yellow colonies, sometimes with tufts of whitish aerial mycelium.⁽¹²⁾ Microscopically *M. faeni* produces chains of spores of 0.8 to 1.5 micrometers in diameter, a size which when inhaled, may penetrate to the extremities of the respiratory airways.⁽¹⁵⁾

Other thermophilic actinomycetes, *S. ulridis*, members of the genus *Thermoactinomyces* and the fungus *Aspergillus fumigatus* also cause sensitization in farmer's lung, although their role in the disease is defined less precisely. In other locations, alternative organisms may be important in disease development, for example, species of the *A. glaucus* group appear to be the most frequent sensitizing agents in Finland.^(16,17)

Clinical aspects of farmer's lung

The acute symptoms of farmer's lung disease and indeed all of the hypersensitivity pneumonitis disorders occur four to eight hours after a heavy exposure to the dust. Typically, symptoms include fever with sweating and chills, a troublesome but often unproductive cough, shortness of breath, and more generalized feelings of malaise with muscle and joint aches. Following an acute episode, such symptoms may resolve within 48 hours or may persist for several weeks. X-ray changes, which appear within days of the episode, show a reticular, nodular pattern of infiltrates throughout the lower two-thirds of the lung fields. These may also resolve in a matter of weeks. In situations where subacute exposure is repeated frequently, a more insidious onset is reported. The chronic disease is characterized by progressively increasing dyspnea, chronic cough, weakness, anorexia, and resultant weight loss. Chronic cases present a spectrum of X-ray abnormalities from the acute picture through to deforming pulmonary fibrosis.

Pulmonary function studies in patients show little or no evidence of obstructive airways disease. The defects principally recorded are reduced lung volumes and impaired diffusing capacity, amounting to a restrictive pulmonary function picture. In long-term sufferers, the disease may result in crippling respiratory insufficiency.

Peripheral tissues, obtained by open lung biopsy, show a characteristic histopathology, almost exclusive to hypersensitivity pneumonitis conditions.^(18,19) The normal structure of respiratory bronchioles and alveoli is destroyed by a mononuclear infiltration of the interstitial tissues, resulting in gross thickening of the alveolar-capillary membranes. Focal concentrations of mononuclear cells forming non-caseating granulomata are a prominent feature and may distort to

occlude bronchiolar airways. Within the areas of inflammation, multinucleated Langerhan's giant cells and foreign body cell types are common. In chronic cases, this pattern may be supplemented with or replaced by a varying degree of fibrosis.

In farmer's lung, the spores of the actinomycetes have not been commonly recognized in the lesions, although particles of indeterminate nature have been reported,⁽¹⁸⁾ and *M. faeni* and *Thermoactinomyces* spp. have been cultured from biopsy tissue.^(20,21) In cases of maple bark stripper's disease, the larger (approximately 4.0 μ) spores of the causative fungus *Cryptostroma corticale* have been identified in the tissues.⁽²²⁾ Such findings do not appear to have diagnostic significance; thermophilic and mesophilic actinomycetes and a variety of fungi have been isolated from biopsy tissue and bronchoalveolar washings from exposed individuals who do not have farmer's lung (unpublished observations).

Prognosis

Once established, a diagnosis of farmer's lung is a permanent acquisition. By virtue of this hypersensitive condition, any further exposure to the offending dust will aggravate the pathogenic processes in the lung. The recurrence of symptoms and the progression of the lung damage is not simply a reflection of the intensity of exposure, but is, moreover, a reflection of the individual's sensitivity. In this respect, therefore, there is probably no threshold level dividing safe from hazardous conditions for the hypersensitivity pneumonitis patient.

Thus, it is clearly important for the physician to be informed of the probable outcome of continued exposure. In the acute form, farmer's lung rarely is fatal, however, this eventuality has been documented.⁽²³⁾ Of greater concern is the progressive respiratory impairment which results from successive acute episodes or the chronic disease. Longitudinal evaluation of a group of farmer's lung patients has revealed that patients who remained on the farm experienced an unquestionable increase in morbidity and mortality rates.⁽²⁴⁾ Those who reported more than five acute episodes had a significantly higher prevalence of permanent lung damage, and 45% of the deaths that occurred in the study group were attributed directly or indirectly to their respiratory disease. These data

supported the previously observed trends that had given rise to the conventional approach to management, that was to advise the patient to leave the farm. However, there was another group of subjects who, through undocumented measures, had managed to avoid recurrence of the disease and permanent disability.

Without further research into the clinical history of farmer's lung, it will not be possible to identify those prone to progression of the disease. Clearly the farmer should not be encouraged to quit until the outcome of his condition can be predicted more precisely. In the meantime, patients must be treated and managed individually according to their progress as indicated by frequent pulmonary evaluations.

Diagnosis

A diagnosis of farmer's lung disease is deduced usually from the patient's history of exposure related symptoms with additional clinical information from X-rays and pulmonary function studies.

For a definitive diagnosis, some demonstration of sensitization to the offending antigen(s) usually is deemed necessary. Serum precipitins to extracts of mouldy hay or to thermophilic actinomycetes, may be detected simply by the Immunodiffusion techniques applied by Pepys and Jenkins,⁽¹³⁾ or as modified by Flaherty and associates.⁽²⁵⁾ While constituting a useful confirmatory criterion, the presence of precipitins to appropriate antigens is not in itself an indication of the disease. Organic dusts are common in the farm environment and 8 to 10% of the exposed population may have such antibodies,^(26,27) but only a small minority of these have evidence of disease.⁽²⁸⁾

The nature of the immunological response to farmer's lung antigens has been examined extensively in order to refine or develop a laboratory test that will allow distinction between the farmer's lung patient and the asymptomatic precipitin positive farmer. These test systems (Table II) have improved variously the detection and quantitation of antibody, and in the case of crossed immunoelectrophoresis⁽²⁹⁾ has demonstrated elegantly the complexity of *M. faeni* antigens and the precipitin response to them. However, none of these assays appear to discriminate between disease and mere sensitization. Similarly, although many

techniques for antigen preparation have been developed, comparisons have shown little improvement in diagnostic efficacy.⁽³⁰⁻³²⁾ Other methods that have been applied to farmer's lung disease, but have failed to show diagnostic capabilities, include tests for cell mediated immunity, response to mitogens, serum complement levels,⁽²⁸⁾ levels of angiotensin converting enzyme,⁽³³⁾ and intradermal skin testing.⁽³⁴⁾

Unquestionable evidence for the diagnosis of farmer's lung can be acquired either by demonstrating a typical histopathology in biopsied lung tissue, or by provoking an episode of the disease. The former approach has been used extensively by Marshfield clinicians, and their experience of 60 farmer's lung biopsies has been documented recently.⁽³⁵⁾ Inhalation challenge is effected by administering controlled doses of aerosolized antigen to the patient who is in a quiescent state of the disease and following the development of clinical symptoms. This latter technique is considered by some authorities to be the definitive diagnostic procedure.⁽³⁶⁻³⁸⁾ However, its success depends upon administering an adequate dose of the appropriate antigen, two factors that are not always well defined.

Neither lung biopsy nor bronchial challenge can be undertaken lightly. Both techniques require hospitalization and some stress, expense, and discomfort for the patient. Furthermore, there are ethical considerations in deciding to provoke

TABLE II
Serological Test Methods Applied to Farmer's Lung Disease

Qualitative Methods
Double immunodiffusion ^(25, 44)
Immunoelectrophoresis ⁽⁴¹⁾
Immunoosmophoresis ⁽⁴²⁾
Counterimmunoelectrophoresis ⁽⁴³⁾
Crossed immunoelectrophoresis ⁽²⁹⁾
Quantitative Methods
Complement fixation ^(41, 46)
Latex agglutination ⁽⁴⁵⁾
Haemagglutination ⁽⁴⁷⁾
Indirect fluorescent antibody ^(48, 49)
Radioimmunoassay ⁽⁵⁰⁾
ELISA (enzyme-linked immunosorbent assay) ^(51, 52)
Crossed immunoelectrophoresis ⁽²⁹⁾

what is a potentially damaging lung disease for the sake of diagnosis.

It seems that there is a continuing need for alternative noninvasive diagnostic procedures. Recent studies of bronchoalveolar lavage fluid from patients with hypersensitivity pneumonitis may represent a step in this direction. Cells are collected from the distal airways of the lung by introducing and withdrawing saline through a bronchoscope. The composition of this population of cells from cases of hypersensitivity pneumonitis is abnormally rich in lymphocytes and seems to reflect the pathological processes in the lung tissues.⁽³⁵⁾

Pathogenesis

The exact nature of the pathogenesis of farmer's lung disease is unclear, and it is beyond the scope of this manuscript to enter into a detailed discussion of the suggested mechanisms. These have been well reviewed.⁽⁴⁰⁻⁴³⁾

Farmer's lung is foremost a hypersensitivity reaction and evidence suggesting any microbial colonization of the lung is sparse and speculative.^(44,45)

Mechanisms of hypersensitivity have been ascribed traditionally to four distinct categories of which two appear to be involved in farmer's lung: immune complex or Arthus reaction (Type III) and cell-mediated (Type IV) hypersensitivity.

Characteristically, Type III reactions are mediated by precipitating antibodies, producing symptoms after a four to eight hour delay. Both features are compatible with those seen in hypersensitivity pneumonitis disorders. Thus, it is postulated that inhaled antigens from hay dust could combine with free antibody in the tissues to form immune complexes which fix and activate the complement cascade. Chemotactic agents released from the components of complement attract alveolar macrophages and polymorphonuclear cells which release the enzymatic contents of their lysosomes onto the membranes of the lung causing tissue damage.

Type IV hypersensitivity reaction is more compatible with the histopathology of hypersensitivity pneumonitis and the involvement of cell mediated immunity has been demonstrated by antigen induced lymphokine release from lung cells of

humans and animal models.^(46,47) In this hypothesis, the sensitized T-lymphocytes are stimulated by inhaled antigen(s) and through the release of lymphokines attract and activate alveolar macrophages. As with a Type III pathogenesis, the tissue damage probably is effected by the hydrolases and oxidases from the macrophage lysosomes. Though each of these mechanisms have proponents, it appears probable that both are involved and interact with a number of feedback mechanisms which serve to amplify the inflammatory processes (Figure 1).

Immunological pathways are considered generally as the principal pathogenic mechanisms. However, aside from their antigenic properties, the thermophilic actinomycetes are attributed with several other important biological properties. Included among these nonspecific factors is the capacity to activate the complement cascade in the absence of specific antibody,⁽⁴⁸⁻⁴⁹⁾ and the potential to cause serum independent enzyme release from macrophage lysosomes.⁽⁵⁰⁾ Both these properties could induce the localized inflammation that appears to be a necessary adjunct to antigen exposure in initiating the histopathology seen in farmer's lung.⁽⁵¹⁾

Other studies have revealed that *M. faeni* organisms possess mitogenic and immunoadjuvant properties which could serve to stimulate the inflammation.⁽⁵²⁻⁵³⁾ Another factor, probably of relevance in farmer's lung disease, is the physical form of the antigen. Experience with animal models has shown that the particulate nature of the causative material enhances its pathogenic potential over soluble antigens.^(47,54,55) The bulk of the causative dust is particulate in the form of actinomycete spores, many of which are relatively insoluble, especially the durable endospores of *Thermoactinomyces* spp.⁽⁵⁶⁾ A final biological activity to be considered for a role in the pathogenesis is the proteolytic capacity of certain enzymes that derive from thermophilic actinomycetes.⁽⁵⁷⁾ Microbial proteinases have been implicated in other hypersensitivity diseases,⁽⁵⁸⁾ and their role as antigens in farmer's lung are recognized.^(59,60) Certain proteinases of thermophilic actinomycetes are not inhibited by human α_1 -antitrypsin⁽⁶²⁾ and, thus, may interact with lung tissues to modify the absorption of antigens, activate effector systems, or, by direct action, cause tissue damage.

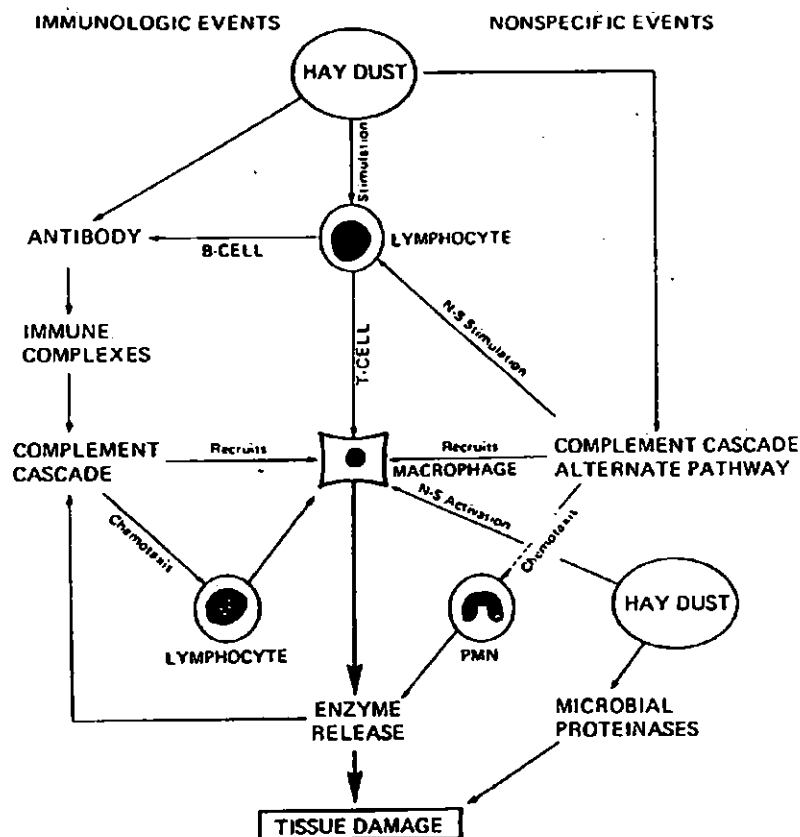


Figure 1 — A simplified flow diagram demonstrating some of the mechanisms purported to be involved in the pathogenesis of farmer's lung disease.

The precise roles played by these immunological and nonspecific mechanisms in pathogenesis remain undefined, but more information from animal models and humans (facilitated by bronchoalveolar lavage) should provide greater insight into the interactions of these postulated mechanisms.

Epidemiology

Farmer's lung disease has a wide distribution throughout countries in the northern temperate zone. Research work and cases have been documented from the United Kingdom, Europe, Scandinavia, and the North American continent.

Epidemiological studies from Britain first drew attention to the prevalence of this disease,⁽⁶³⁾ but the results of this and subsequent surveys are difficult to compare and interpret because of the following inconsistencies:

1. Study populations have all varied considerably in composition, some based solely on cases seeking medical treatment,⁽⁶³⁻⁶⁵⁾ others from cross-sectional surveys variously including or excluding the farmer's families.^(66,67)
2. The criteria used for identifying cases also differ, giving more or less emphasis to clinical, historical, and serological evidence, highlighting the continuing need for reliable and diagnostic laboratory tests.
3. Farmer's lung is a seasonal disease.⁽⁶⁸⁻⁶⁹⁾ While symptoms are not restricted totally to winter and spring, diagnosis is most common during this period when livestock and farmwork are confined largely to the barn. Thus, surveys and examinations conducted in the summer and autumn may reflect the observation that both symptoms and memories may be short-lived.

All the above variables conspire to modify the resulting figures of prevalence and, thus, may mask their potential value for assessing the effects of regional weather and farming practices on the incidence of farmer's lung.

The earliest estimations of prevalence rates in areas of Great Britain, based upon cases seen and recognized by medical practitioners,⁽⁶³⁾ were 1.9/1000 farmers in Wales, 0.73/1000 in S.W. England, and 0.115/1000 in East Anglia where the rainfall is lower and dairy farming is less common. Later studies of farming populations, selected by a cross-sectional survey, gave markedly higher prevalence rates: 54/1000 for Wales and 22/1000 for Devon, a county in S.W. England.⁽⁶⁷⁾

The results from a pilot survey of farmers in three areas of Scotland, based on symptoms and history, were 86/1000 for two regions, and 23/1000 for the third. However, when a positive serological reaction to *M. faeni* or *T. vulgaris* was included as a necessary criterion for farmer's lung diagnosis, these prevalence rates fell to 43, 36, and 0/1000 farmers, respectively.⁽⁶⁶⁾

Surveys in the United States have given generally much lower prevalence rates for farmer's lung disease. Roberts reported that 8.9% of attendees at a farm progress exposition, who volunteered blood samples, were sensitized to one or more of a panel of farmer's lung antigens.⁽²⁶⁾ Further evaluation of a subgroup of these sensitized farmers disclosed consistent histories in 38%, but no cases of active disease.⁽²⁸⁾ In western Wyoming, 5.1% of a farming population reported compatible symptoms, but with corroborating clinical and serological evidence the recalculated prevalence was 7.3 cases/1000.^(27,70) From Vermont a figure of 3.9/1000 farmers has been given.⁽⁷¹⁾

In a recently completed random, cross-sectional survey conducted from Marshfield, Wisconsin, data on 1444 adults from 632 farms were collected by questionnaire and serological studies.⁽²⁷⁾ Approximately 10% of the population showed precipitins to at least one of an appropriate panel of antigens used in this study as a conditional prerequisite for a diagnosis of farmer's lung. Further clinical evaluation of this group revealed six cases of the disease to give a prevalence of 4.2/1000 with a slightly higher rate for men than for women. An analysis of risk factors revealed that full-time farmers with larger farms (average 213 to 405

acres), more head of cattle, and a larger acreage of hay and oats as opposed to corn and pasture, had the highest likelihood of developing disease.

This study from central Wisconsin also emphasized an interesting association between farmer's lung and cigarette smoking that has been noted by others.^(67,70,72) In contrast to other lung diseases, farmer's lung among non-smokers was 6.1/1000, while no cases were found among current smokers. Former smokers showed an intermediate prevalence rate. A similar relationship was also noted between smoking and antibody elaboration to *M. faeni* antigens. Six percent of the population had precipitins to this organism, and the prevalence of sensitization was eight times higher in non-smokers and six times higher in former smokers than among current smokers.

This relationship between smoking, antibody, and disease development is particularly intriguing. Gruchow and colleagues⁽²⁷⁾ have postulated that either smoking may be protective of farmer's lung or there may be a self-selection against smoking in people prone to the disease. An explanation for this phenomenon must await further research on the interaction of tobacco smoke and the lung's immune function. This topic certainly seems prime for further study, as smoking appears to offer a model for prophylactic treatment in farmer's lung.

Atypical or precipitin-negative farmer's lung

Epidemiological studies of farmer's lung in Britain and in the U.S. have identified groups of individuals who report symptomatic episodes consistent with the disease, but who lack the precipitins which are considered an integral part of the syndrome.^(66,70) It seems likely that these groups represent cases of a disease different from the "classical" form of farmer's lung which will be referred to as "atypical farmer's lung." Originally described by Emanuel from Marshfield and tentatively called pulmonary mycotoxicosis,⁽⁷³⁾ it also has been termed precipitin-negative farmer's lung.⁽⁴⁸⁾

Atypical farmer's lung is not considered to be a hypersensitivity pneumonitis, but results from similar circumstances, most commonly following dust exposure while "uncapping" a silo. In Wisconsin, cattle fodder is often stored in silos and in

TABLE III
Atypical Farmer's Lung: Cases and the Causative Materials

Material	Number of Cases	Percent (Where Specified)
Haylage	43	60.0
Oats	16	22.5
Cornlage	10	14.1
High moisture ear corn	1	1.4
Shelled corn	1	1.4
Sub-total	<u>71</u>	
Unspecified	<u>22</u>	
Total	93	

order to provide anaerobic conditions necessary for preservation, the exposed surface commonly is covered with a plastic sheet held in place with a further layer of moist forage. This top layer invariably undergoes extensive moulding, and in silos that are not "sealed" with plastic, the top foot or so becomes spoiled and must be removed. "Uncapping" a silo involves manually throwing off the dry, dusty material, removing the plastic sheet and any spoiled silage beneath to uncover the moist fodder which then can be unloaded mechanically and fed to the cattle. During this process, much dust may be generated. Some 90 cases of atypical farmer's lung have been seen at the Marshfield Clinic over the last decade, and the most common documented cause has been uncapping silos of haysilage, although other mouldy materials also have been responsible (Table III).

The symptoms of this disorder are almost identical to those of an acute episode of classical farmer's lung with a delayed onset of fever, cough, dyspnea, myalgia, and arthralgia.

There are, however, several features that serve to distinguish this condition from classical farmer's

lung disease (Table IV). The episodes occur only after intense dust exposure; one case resulted from 45 minutes exposure to total dust levels of 106 mg/m^3 with a respirable dust ($< 5.5 \mu$) level of 57 mg/m^3 , as measured with an Andersen sampler.⁽⁷⁴⁾ The symptoms usually resolve within 10 days, whereas in hypersensitivity pneumonitis, continued exposure even at a low level may cause symptoms to persist and the disease to progress to the chronic form. There appear to be no host factors involved, as groups of three or more people exposed in one incident usually experience the same symptoms. A history of previous exposures, or evidence of immunological sensitization is not a prerequisite for atypical farmer's lung. Precipitins to farmer's lung antigens generally are absent, but are detected more frequently in this group than in the general farming population. Finally, recent evidence from bronchoalveolar lavage studies has shown that the principal cells recovered from atypical cases are polymorphonuclear leukocytes, while in classical farmer's lung the lymphocyte predominates.⁽⁷⁵⁾

The assemblage of evidence listed supports the opinion that atypical farmer's lung is a distinct pathological entity characterized by an acute inflammatory reaction to components of the dust. Edwards and colleagues have proposed the dust's capacity to activate complement by the alternative pathway as a probable cause and mechanism for the disorder.⁽⁴⁸⁾ Alternative hypotheses suggest roles for endotoxin, mycotoxins, and/or microbial proteinases. Currently, we are characterizing the microbial populations in capping haylage dusts, but at this time have not defined any microbiological parameter to distinguish the causative dusts from controls.⁽⁷⁶⁾

Atypical farmer's lung does not appear to have such severe implications as the classical disease.

TABLE IV
Differences Between "Classical" and "Atypical" Farmer's Lung

	"Atypical"	Classical"
Exposure level	High	Low or high
Progressive disease	None	With further exposure
Selectivity	All exposed individuals	Susceptible individuals only
Serology	Generally negative	Positive
Predominant lung lavage cells	Polymorphonuclear neutrophils	Lymphocytes

It occurs only under exceptionally heavy dust exposure and seems to resolve completely. However, the questions it raises about a possible relationship between atypical and classical farmer's lung are intriguing. Could this acute reaction represent the initial inflammatory response and sensitizing dose of antigen that leads to the development of classical farmer's lung disease? Is the acute form of hypersensitivity pneumonitis merely an atypical episode superimposed on the chronic disease? These questions merit further study.

Treatment and control

Farmer's lung disease cannot be cured. Once a subject has developed the hypersensitivity, episodes of symptoms or progression to chronic lung disease will result from repeated exposure to dusts containing the specific antigens, whatever their source. In severe cases, the resolution of the symptoms may be enhanced by administering corticosteroids. Empirically, such treatment has given good results, probably due to the drug's stabilizing influence on macrophage lysosomal membranes. This short-term therapy must be accompanied by a sustained effort to avoid further exposure to mouldy or dusty agricultural produce.

Avoiding organic dusts is advisable not only for patients, but should be practiced by all farm workers as a preventive measure. Since the root of the problem is the moisture content of stored cereals and forage which dictates the extent of overheating and moulding, the farmer can minimize the chance for subsequent harmful dust exposure by carefully monitoring this variable. Alternative forms of storage for crops, such as ensiling hay, should be encouraged. Silo storage certainly will limit moulding to the aerobic areas, and these can be reduced by careful silage distribution and sealing with an intact plastic sheet tucked in around the silo walls and secured with a minimum of extra material. Once uncapped, silage may be unloaded and fed mechanically with little need for physical contact. Sophisticated, glass lined, oxygen limiting silos that unload from the base obviate the need for capping and uncapping and, thus, eliminate any dust problems.

An alternative approach to prevent moulding is the use of organic acid additives. Propionic acid appears to have the potential to reduce over-

heating significantly and to limit the development of *M. faeni* in hay baled with a high moisture content.⁽⁷⁷⁾ However, there exist technical difficulties in applying such materials evenly to the crops.

In circumstances where changes in farm practices and avoidance of dusts are insufficient to prevent recurrent or continuing disease, dust respirators or face masks have been used effectively.^(78,79) A respirator should be chosen that is capable of handling high levels of dust in the one micron particle size range, and yet provides minimal resistance for hard work situations. It should provide a good seal around the mouth and nose, and must be maintained in an effective working condition. Finally, the personal choice of the individual and his ability to tolerate wearing a respirator for lengthy work periods must be considered.

Ignorance of the potential hazards posed by mouldy crops remains the greatest barrier to be overcome in the eradication of farmer's lung. Were this disease to occur in a localized industrial workplace, the size of the farming population, the attention generated would spur on the search for better methods of control. Exposure to dusts is accepted too readily as part of the job, and this complacent attitude can be changed only by a concerted program of official propaganda and education. Hopefully, this symposium may mark a turning point in the amount of emphasis placed upon the hazards faced by the farmer and in our efforts to make his job safe. For, after all, in the words of Woody Guthrie, "The farmer is the man who feeds us all," and his health should be our concern.

References

1. Ramazzini, B.: *De Morbis Artificum Diatriba* (1713). Translated by W.C. Wright, Univ. Chicago Press, Chicago, IL (1940).
2. Campbell, J.M.: Acute Symptoms Following Work with Hay. *Brit. Med. J.* 2:1143 (1932).
3. Butcher, B.T., J.E. Salvaggio, H. Weill and M.M. Ziskind: Toluene Diisocyanate (TDI) Pulmonary Disease: Immunologic and Inhalation Challenge Studies. *J. Allergy Clin. Immunol.* 58:89 (1976).
4. Zeiss, C.R., R. Patterson, J.J. Pruzansky et al: Trimellitic Anhydride (TMA) Induced Airway Syndromes: Clinical and Immunologic Studies. *Ibid.* 60:96 (1977).
5. Gregory, P.H. and M.E. Lacey: Mycological Examination of Dust from Mouldy Hay Associated with Farmer's Lung Disease. *J. Gen. Microbiol.* 30:75 (1963).

6. Gregory, P.H., M.E. Lacey, G.N. Festenstein and F.A. Skinner: Microbial and Biochemical Changes During the Moulding of Hay. *Ibid.* 33:147 (1963).
7. Gregory, P.H., G.N. Festenstein, M.E. Lacey et al: Farmer's Lung Disease. The Development of Antigens in Moulding Hay. *Ibid.* 36:429 (1964).
8. Gregory, P.H. and M.E. Lacey: Isolation of Thermophilic Actinomycetes. *Nature* 195:95 (1962).
9. Lacey, J. and J. Dutkiewicz: Isolation of Actinomycetes and Fungi from Mouldy Hay using a Sedimentation Chamber. *J. Appl. Bacteriol.* 41:315 (1976).
10. Lacey, J. and M.E. Lacey: Spore Concentrations in the Air of Farm Buildings. *Trans. Brit. Mycol. Soc.* 47:547 (1964).
11. Lacey, J.: The Microbiology of Moist Barley Storage in Unsealed Silos. *Ann. Appl. Biol.* 69:187 (1971).
12. Cross, T., A.M. Maciver and J. Lacey: The Thermophilic Actinomycetes in Mouldy Hay: *Micropolyspora faeni* sp. nov. *J. Gen. Microbiol.* 50:351 (1968).
13. Pepys, J. and P.A. Jenkins: Precipitin (FLH) Test in Farmer's Lung. *Thorax* 20:21 (1965).
14. Wenzel, F.J., R.L. Gray, R.C. Roberts and D.A. Emanuel: Serologic Studies in Farmer's Lung. Precipitins to the Thermophilic Actinomycetes. *Am. Rev. Resp. Dis.* 109:464 (1974).
15. Mulr, D.C.F.: Deposition and Clearance of Inhaled Particles. *Clinical Aspects of Inhaled Particles*, pp. 1-20. Heinemann, London (1972).
16. Terho, E.O. and J. Lacey: Microbiological and Serological Studies of Farmer's Lung in Finland. *Clin. Allergy* 9:43 (1979).
17. Katila, M.L. and R.A. Mantijarvi: The Diagnostic Value of Antibodies to the Traditional Antigens of Farmer's Lung in Finland. *Ibid.* 8:581 (1978).
18. Emanuel, D.A., F.J. Wenzel, C.I. Bowerman and B.R. Lawton: Farmer's Lung. Clinical, Pathologic and Immunologic Study of 24 Patients. *Am. J. Med.* 37:394 (1964).
19. Seal, R.M.E., E.J. Hapke, G.O. Thomas et al: The Pathology of the Acute and Chronic Stages of Farmer's Lung. *Thorax* 23:469 (1968).
20. Wenzel, F.J., D.A. Emanuel, B.R. Lawton and G.E. Magrin: Isolation of the Causative Agent of Farmer's Lung. *Ann. Allergy* 22:533 (1964).
21. Wenzel, F.J., D.A. Emanuel and B.R. Lawton: Pneumonitis due to *Micromonospora vulgaris* (Farmer's Lung). *Am. Rev. Resp. Dis.* 95:652 (1967).
22. Emanuel, D.A., F.J. Wenzel and B.R. Lawton: Pneumonitis due to *Cryptosporidia corticale* (Maple Bark Disease). *New Eng. J. Med.* 247:1413 (1966).
23. Barrowcliff, D.F. and P.G. Arblaster: Farmer's Lung: A Study of an Early, Acute Fatal Case. *Thorax* 23:490 (1968).
24. Braun, S.R., G.A. doPico, A. Tsiatis et al: Farmer's Lung Disease: Long-term Clinical and Physiologic Outcome. *Am. Rev. Resp. Dis.* 119:185 (1979).
25. Flaherty, D.K., J. Barboriak, D.A. Emanuel et al: Multilaboratory Comparison of Three Immunodiffusion Methods Used for the Detection of Precipitating Antibodies in Hypersensitivity Pneumonitis. *J. Lab. Clin. Med.* 84:298 (1974).
26. Roberts, R.C., F.J. Wenzel and D.A. Emanuel: Precipitating Antibodies in a Midwest Dairy Farming Population Toward the Antigens Associated with Farmer's Lung Disease. *J. Allergy Clin. Immunol.* 57:518 (1976).
27. Gruchow, H.W., R.G. Hoffmann, J.J. Marx, Jr. et al: Precipitating Antibodies to Farmer's Lung Disease Antigens in a Wisconsin Farming Population. *Am. Rev. Resp. Dis.* 124:411 (1981).
28. Marx Jr., J.J., D.A. Emanuel, W.V. Dovenbarger et al: Farmer's Lung Disease among Farmers with Precipitating Antibodies to the Thermophilic Actinomycetes: A Clinical and Immunologic Study. *J. Allergy Clin. Immunol.* 62:185 (1978).
29. Treuhaff, M.W., R.C. Roberts, C. Mackbarth et al: Characterization of Precipitin Response to *Micropolyspora faeni* in Farmer's Lung Disease by Quantitative Immunoelectrophoresis. *Am. Rev. Resp. Dis.* 119:571 (1979).
30. Dick, H., C.O. Dawson and J.D. Campbell: Farmer's Lung: A Comparison of Simple Diagnostic Techniques and Antigen Preparation in Human and bovine Disease. *Clin. Allergy* 3:209 (1973).
31. Hollingdale, M.R.: Antibody Responses in Patients with Farmer's Lung Disease to Antigens of *Micropolyspora faeni*. *J. Hygiene* 72:79 (1974).
32. Roberts, R.C., D.P. Zais and D.A. Emanuel: The Frequency of Precipitins to Trichloroacetic Acid Extractable Antigens from Thermophilic Actinomycetes in Farmer's Lung Patients and Asymptomatic Farmers. *Am. Rev. Resp. Dis.* 114:23 (1976).
33. Tewksbury, D.A., J.J. Marx, Jr., R.C. Roberts and D.A. Emanuel: Angiotensin-Converting Enzyme in Farmer's Lung. *Chest* 79:102 (1981).
34. Freedman, P.M., B. Ault, C.R. Zeiss et al: Skin Testing in Farmer's Lung Disease. *J. Allergy Clin. Immunol.* 67:51 (1981).
35. Reyes, C.M., F.J. Wenzel, B.R. Lawton and D.A. Emanuel: The Pulmonary Pathology of Farmer's Lung Disease. *Chest* (In press).
36. Schleuter, D.P.: Response of the Lung to Inhaled Antigens. *Am. J. Med.* 57:476 (1974).
37. Pepys, J.: Farmer's Lung as an Occupational Disease (Roundtable). *Aspergillosis and Farmer's Lung in Man and Animals*, R. deHaller and F. Suter, Eds., p. 320. Davos Symposium, Hans Huber, Bern (1974).
38. Fink, J.N.: The Use of Bronchoprovocation in the Diagnosis of Hypersensitivity Pneumonitis. *J. Allergy Clin. Immunol.* 64:590 (1979).
39. Reynolds, H.Y., J.D. Fulmer, J.A. Kazmierowski et al: Analysis of Cellular and Protein Content of Broncho-Alveolar Lavage Fluid from Patients with Idiopathic Pulmonary Fibrosis and Chronic Hypersensitivity Pneumonitis. *J. Clin. Invest.* 59:165 (1977).
40. Roberts, R.C. and V.L. Moore: Immunopathogenesis of Hypersensitivity Pneumonitis. *Am. Rev. Resp. Dis.* 116:1075 (1977).
41. Lopez, M. and J.E. Salvaggio: Hypersensitivity Pneumonitis: Current Concepts of Etiology and Pathogenesis. *Ann. Rev. Med.* 27:453 (1976).
42. Schatz, M., R. Patterson and J.N. Fink: Immunopathogenesis of Hypersensitivity Pneumonitis. *J. Allergy Clin. Immunol.* 60:27 (1977).
43. Salvaggio, J.E.: Immunological Mechanisms in Pulmonary Diseases. *Clin. Allergy* 9:659 (1979).
44. Edwards, J.H.: The Antigenic Background of Farmer's Lung. *Tubercle* 51:218 (1970).
45. Greathorex, F.B. and J. Pether: Cough in Farmer's Lung Disease. *Brit. Med. J.* 1:303 (1978).

21 MARS 1988

Reprint

Publishers: S. Karger, Basel
Printed in Switzerland

Monogr. Allergy, vol. 21, pp. 70-86 (Karger, Basel 1987)

Epidemiology of Hypersensitivity Pneumonitis/Allergic Alveolitis

Manuel Lopez, John E. Salvaggio

Department of Medicine, Tulane University School of Medicine,
New Orleans, La., USA

Hypersensitivity pneumonitis (HP) or extrinsic allergic alveolitis represents a group of immunologically induced diseases associated with intense and/or repeated exposure to finely dispersed organic dusts that affect the distal portion of the lung [1-3]. Although there are many types of hypersensitivity pneumonitis, the clinical and pathological findings are similar regardless of the inhaled organic dust. Clinically, affected patients have episodes of fever, cough and dyspnea 4-6 h following exposure to the appropriate organic dust (e.g. hay, bagasse, pigeon droppings). Symptoms are frequently mistaken for those of bacterial or viral pneumonia. In the most insidious cases associated with prolonged exposure to smaller quantities of the antigen an afebrile chronic form of the disease may occur. This chronic form is associated with cough, dyspnea, malaise, weakness, and weight loss. Pulmonary function abnormalities range from diffusion defects to varying degrees of restrictive and obstructive dysfunction. Changes similar to those found in emphysema may be seen in patients with chronic disease.

Etiology

There are numerous causes of hypersensitivity pneumonitis (table I). The majority of recognized etiologic agents are derived from occupational exposure such as farming, sugar cane harvesting, working with cereal grains or wood products, and packing mushrooms. The disease may also result from exposure to contaminated central heating and humidification units or may be related to hobbies, such as pigeon breeding. Offending antigens may be derived from microorganisms (actinomycetes, bacteria, fungi, amoebae),

animal and plant products, small molecular weight chemicals, and some pharmaceutical products.

Histopathology

Most varieties of hypersensitivity pneumonitis are characterized by similar histologic changes which largely depend on the intensity of antigen exposure and on the stage of the disease at the time of the biopsy. The more common tissue reaction in acute cases consists of alveolar and interstitial inflammation, with marked prominence of lymphocytes, plus increased numbers of plasma cells, and activated macrophages. A frequent pathologic feature is the presence of macrophages with foamy cytoplasm. Giant cells are often seen, some of which may contain birefringent material. After several months, subacute disease may develop, in some cases characterized by noncaseating granulomas that closely resemble those found in sarcoidosis. In the chronic stage, the granulomas either persist or disappear and interstitial fibrosis may develop. The fibrosis may be localized, forming focal areas or may be more diffuse causing microcysts similar to those of fibrosing alveolitis. The upper zones of the lung are usually more affected.

Diagnosis

There is not a single clinical finding or laboratory test diagnostic of the disease. A carefully obtained clinical history suggesting a possible temporal relationship between symptoms and certain activities such as entering a building, working with hay, or engaging in a particular hobby may provide a clue to the presence of sensitization. This may be complemented by demonstrating remission of symptoms following extended removal from the antigen source. In the final analysis the diagnosis is made by a combination of clinical findings, X-ray abnormalities, pulmonary function and immunologic tests. Inhalation challenge and lung biopsy may be necessary to confirm the presence of the disease.

Epidemiology

Epidemiological studies are concerned with patterns of disease and the factors that influence these patterns.

Table 1. Etiology of hypersensitivity pneumonitis

Disease	Source of antigen	Probable antigen
<i>Vegetable Products</i>		
Farmer's lung disease	moldy hay	<i>Thermophilic actinomycetes</i> , <i>M. faeni</i> , <i>T. vulgaris</i> , <i>Aspergillus</i> sp.
Bagassosis	moldy pressed sugar cane (bagasse)	<i>Thermophilic actinomycetes</i> , <i>T. sacchari</i> , <i>T. vulgaris</i>
Mushroom worker's disease	moldy compost	<i>Thermophilic actinomycetes</i> , <i>M. faeni</i> , <i>T. vulgaris</i>
Suberosis	moldy cork	<i>Penicillium</i> sp.
Malt worker's lung	contaminated barley	<i>Aspergillus clavatus</i>
Maple bark disease	contaminated maple logs	<i>Cryptostroma corticale</i>
Sequoiosis	contaminated wood dust	<i>Graphium</i> sp., <i>Pullularia</i> sp.
Wood pulp worker's disease	contaminated wood pulp	<i>Alternaria</i> sp.
Humidifier lung	contaminated humidifiers, dehumidifiers, air conditioners	<i>Thermophilic actinomycetes</i> , <i>T. candidus</i> <i>T. vulgaris</i> , <i>Penicillium</i> sp., <i>Cephalosporium</i> sp., amoebae
Familial hypersensitivity pneumonitis	contaminated wood dust in walls	<i>Bacillus subtilis</i>
Cheesewasher's disease	cheese casings	<i>Penicillium</i> sp.
Wood trimmer's disease	contaminated wood trimmings	<i>Rhizopus</i> sp., <i>Mucor</i> sp.
Thatched roof disease	dried grasses and leaves	<i>Saccharomonospora viridis</i>
Tea grower's disease	tea plants	unknown
Coffee worker's lung	green coffee	unknown
Streptomyces hypersensitivity pneumonia	contaminated fertilizer	<i>Streptomyces albus</i>
Cephalosporium hypersensitivity pneumonitis	contaminated basement (sewage)	cephalosporium
Sauna taker's disease	sauna water	<i>Pullularia</i> sp.
Detergent worker's disease	detergent	<i>Bacillus subtilis</i> enzymes

Table I. (cont.)

Disease	Source of antigen	Probable antigen
Paprika splitter's lung	paprika dust	mucor stolonifer
<i>Animal products</i>		
Pigeon breeder's disease	pigeon droppings	altered pigeon serum (probably IgA)
Duck fever	duck feathers	duck proteins
Turkey handler's disease	turkey products	turkey proteins
Laboratory worker's hypersensitivity pneumonitis	rat fur	male rat urine
Pituitary snuff taker's disease	pituitary powder	bovine and porcine proteins
<i>Insect products</i>		
Miller's lung	wheat weevils	<i>Sitophilus granarius</i>
<i>Reactive simple chemicals</i>		
TDI hypersensitivity pneumonitis	toluene di-isocyanate	altered proteins (albumin + others)
TMA hypersensitivity pneumonitis	trimetallic anhydride	altered proteins
MDI hypersensitivity pneumonitis	diphenylmethane di-isocyanate	altered proteins
Epoxy resin lung	heated epoxy resin	phthalic anhydride

The manner by which inhaled organic dust induces lesions in hypersensitivity pneumonitis depends on a complex interrelationship between environmental, genetic and other host-related factors. A discussion of the pathogenesis of HP is beyond the purview of this article and the reader is referred to recent discussions of immunopathogenesis and genetics of the disease [4].

Etiologic Agents and Environmental Factors

Etiologic Agents. Various thermophilic and mesophilic actinomycetes including *Micropolyspora faeni*, and the *Thermoactinomyces* species *vulgaris*, *sacchari* and *candidus* may cause disease in situations related to such diverse occupational or nonoccupational factors as the use of home central air conditioning and humidification, farming, mushroom growing, wood cutting and sugar cane processing. Actinomycetes are members of the true bacteria (Eubacteriales), although they have the morphology of fungi and are often mistaken and identified as such. They grow best in decaying organic matter such as hay and bagasse, under optimal conditions of humidity at temperatures between 37 and 60 °C. High numbers of spores are present in contaminated material; Gregory and Lacey [5] have reported studies showing the presence of up to 1.6×10^9 actinomycete spores in the air after disturbing moldy hay. Since particle sizes are smaller than 6 microns, it has been estimated that a farmer working in this environment might inhale and retain in his lung 750,000 spores per minute [6]. Although thermophilic actinomycetes grow abundantly in composts, they are ubiquitous and can be found in soil, foods, fresh water, the atmosphere, and many other natural sources. Proteins derived from feathers, serum, and excrement of several avian and rodent species are also important causes of hypersensitivity pneumonitis.

Organic dusts producing the disease have been found to exert a variety of biological effects. In addition to acting as sources of antigen and eliciting hypersensitivity responses, they can act as adjuvants [7] and thus promote the development of humoral and cell-mediated immunity. They may also activate alveolar macrophages [8] and directly activate the alternative complement pathway [9] providing the necessary stimuli for increased vascular permeability and chemotactic migration of polymorphonuclear leukocytes and macrophages to the lungs. These materials also contain enzymes [10], endotoxins [11] and histamine releasers [12]. The inflammatory consequences of these nonspecific injurious effects and those modulated by

complement and macrophages could be important factors in the pathogenesis of hypersensitivity pneumonitis.

Environmental Factors. Exposure to the offending agents are usually related to occupations or hobbies. The concentration of these agents in a given environment varies significantly according to climatic, meteorologic and local conditions. For example, actinomycetes grow in hay and bagasse under conditions of high humidity and temperature. For this reason the concentration of actinomycetes per pound of hay or bagasse is significantly lower if the material has not been wet or submitted to high temperature. Contamination of humidifiers is very likely related to the humidifiers intrinsic water dispersal system and particularly the frequency in cleaning of the system. Exposure in the work setting may vary among the different workers depending on the place at work in relation to the source of antigenic material.

At the present time there is little information regarding the levels of exposure necessary to cause hypersensitivity pneumonitis in susceptible individuals.

Host Factors

Characteristics of Patients. Although exposure to offending antigens may be almost universal in some occupations and there is a high incidence of precipitating antibodies against the antigens in exposed individuals, the incidence of the disease is low (less than 10% of exposed subjects). The factors that differentiate between symptomatic and asymptomatic exposed subjects are not clear. An attractive theory of susceptibility implicates genetic factors presumably linked to the HLA system. However, several studies have failed to demonstrate any association between specific HLA antigens and susceptibility to disease. A study by Rodey et al. [13] in pigeon breeder's disease did not demonstrate any significant association between any HLA specificity and symptoms. Similar results were obtained by Flaherty et al. [14] in farmer's lung patients and by Muers et al. [15] in patients with budgerigar fancier's lung. At present, any HLA-associated genetic predisposition for the development of hypersensitivity pneumonitis in man remains to be demonstrated. Immunoregulatory events have recently assumed the forefront in animal models of hypersensitivity pneumonitis. Among the recent findings of these studies that have provided new insights

are the following: (1) Certain immunosuppressive agents such as cyclophosphamide can actually enhance rather than suppress the development of granulomatous pneumonitis in certain strains of mice. (2) It appears that a cyclophosphamide-sensitive suppressor T cell regulates the development of pulmonary granuloma formation in this species. (3) The intensity of pulmonary granuloma formation in this species appears to be genetically determined and is a dominant and polygenic trait, since inbreeding studies involving different strains reveal that the F-1 hybrids are responders, and the F-2 hybrids do not segregate into 2 distinct populations. (4) The degree of granuloma formation appears to be linked to the immunoglobulin heavy-chain locus (IgH), because inbreeding studies reveal that most high-responder mice inherit the IgH allotype of the high-responder strains. (5) Anergy has also been shown to develop in a BCG-induced mouse model of hypersensitivity pneumonitis and appears to be a recessive and unigenic trait also linked to the IgH complex. The cells that mediate anergy are adherent cells and are thought to be macrophages. In man, some recent evidence from studies of so-called Japanese type, summer-type hypersensitivity pneumonitis also indicates that patients with active disease are anergic [16].

Thus, there is now increasing evidence that animals lacking high levels of antigen-specific suppressor cell activity can develop pulmonary granulomatous inflammation as a consequence of T cell-mediated hypersensitivity, while low-responder strains develop suppressor cells that modulate the degree of granulomatous inflammation. After granuloma development, anergy, which is also under genetic control by genes linked to the IgH allotype, appears and may be mediated via macrophages directed to be suppressive by T lymphocyte-derived factors. These facts notwithstanding, the genetic factor or factors which predispose toward development of hypersensitivity pneumonitis in man following equivalent exposure to organic dust exposure are not known at the present time.

Precipitating Antibodies. Most patients with HP demonstrate precipitating antibodies directed against the offending organic dust or animal protein antigen. For example, precipitins against extracts of the thermophilic actinomycete *Thermoactinomyces sacchari* have been demonstrated in most patients with active bagassosis [17].

Precipitins against pigeon serum and crude pigeon dropping extracts have been reported in most symptomatic pigeon breeder's disease [18] and approximately 90% of patients with farmer's lungs have precipitating antibodies to thermophilic actinomycetes particularly *Micropolyspora faeni* [1].

However, a significant percentage of farmers exposed to moldy hay, and of sugar cane processing workers exposed to bagasse, who had no history suggestive of the diseases also demonstrated precipitins to moldy hay and bagasse antigens, respectively. As many as 40% of exposed but asymptomatic pigeon breeders also demonstrated precipitins to pigeon serum [19]. Likewise, studies of bronchoalveolar lavage cells from patients in recovering phases of HP have demonstrated large numbers of suppressor cytotoxic and helper T cells with the suppressor subset predominating. Elevated numbers and percentages of suppressor/cytotoxic T cells are, however, present in lavage fluids of asymptomatic persons exposed to antigen as well as those exposed who develop clinical disease. In contrast, precipitins against organic dust antigens and lavage fluid lymphocyte numbers in the normal population are low. In a study by Chmelik and Reed [20] of a total of 1,684 serum samples from office workers and hospitalized patients, the frequency of serum-precipitating antibodies to thermophilic actinomycetes was 3% and pigeon serum 1%. Using the more sensitive technique of counterimmunoelectrophoresis we have reported an incidence of positive precipitins against thermophilic actinomycetes in 12% of 28 medical students from Louisiana [21]. Pepys and Jenkins [22] reported positive precipitins to *M. faeni* in 18% of 28 healthy exposed farmers in England [22]. Roberts et al. [23] in a survey of serum samples from 1,045 Wisconsin farmers attending an exposition, reported an 8.4% incidence of positive precipitins against thermophilic actinomycetes and Gump et al. [24] reported a 6.6% incidence of precipitins to a panel of thermophilic actinomycetes in 260 randomly selected Vermont farmers.

Epidemiologic Studies

Currently, there are no extensive epidemiologic studies on the prevalence of hypersensitivity pneumonitis. Several reasons may be given for the difficulty in performing these types of studies. Hypersensitivity pneumonitis represents a group of syndromes rather than a disease with a single etiologic agent. There is also a lack of agreement regarding the diagnostic criteria needed for planning and carrying out epidemiologic studies on the prevalence of the disease in a given population. To rely on clinical symptoms alone as the basis for identifying patients with the disease is of little specificity. On the other hand, the use of chest roentgenograms, biopsies and inhalation challenge studies to establish diagnosis is impractical for large epidemiologic

studies. The use of precipitins or bronchial lavage studies as markers of the disease activity rather than exposure to antigen per se has not been useful since a significant percentage of exposed individuals have precipitating antibodies against the offending antigen and/or elevated lavage T cell numbers and no evidence of disease. Positive precipitins against a given organic dust antigen and elevated T cell numbers in a group of individuals seem to be clearly related to exposure rather than overt disease activity. With these limitations in mind, we will review some of the published data regarding the distrib

pneumonitis, namely farmer's lung, humidifier lung, pigeon breeder's disease, maple bark disease, and bagassosis, and some of the factors that affect this distribution.

Farmer's Lung

This is the most common type of hypersensitivity pneumonitis, caused by the inhalation of thermophilic actinomycete spores from contaminated hay. At the present time there are no definitive data regarding the prevalence of farmer's lung. The true published incidence may be underestimated due to difficulties in establishing diagnostic criteria. For example, studies by Solal-Celigny et al. [25] demonstrated that some dairy farmers with positive precipitins manifested acute lung disease. Others had positive precipitins but were free from respiratory symptoms, yet they had evidence of alveolitis when pulmonary lavage cells were analyzed. Two of the patients with negative precipitins and no symptoms had evidence of alveolitis.

The prevalence of farmer's lung varies from country to country and within a country, depending on the local geographic and atmospheric conditions. Most of the few studies on the prevalence of the disease have been carried out in Britain and Scotland. Grant et al. [26] performed a pilot study in two farming communities in Scotland. Two counties were chosen, one in the west (Ayrshire) with a high rainfall and another in the east (East Lothian) with a low rainfall. These investigators used a symptom-based criterion for the diagnosis of farmer's lung. The prevalence of farmer's lung symptoms was 8.65 per 100 farmers in Ayrshire and 2.3 per 100 farmers in East Lothian. The authors attributed this regional variation in prevalence to climatic conditions as well as differences in agricultural methods, particularly efficient drying of hay before storage, more extensive use of silage and use of mechanical feeding systems in the farms of East Lothian. Staines and Forhman [27], in a farmer's lung survey, showed an association between the disease and wet climate. They demonstrated that the condition was virtually

unknown in the dry eastern area of England and Scotland but increasingly common in the west areas where the yearly rainfall was high. Data from a postal survey of 12,056 farmers in Finland [28] demonstrated a prevalence of farmer's lung symptoms of 1.6%. Precipitins to thermophilic actinomycetes were positive in 9.2% of 2,470 sera tested. Mastrangelo et al. [29] have reported an incidence of farmer's lung symptoms in 1.3% of farmers in a farming community in Italy and Shelley et al. [30] reported an incidence of 2.6% in farmers in West Ireland. According to Emanuel and Kryda [31], following a summer with heavy rainfall, there was a greater likelihood of the disease in the ensuing winter months. Most cases occur during the late winter and early spring and are probably related to the feeding of the first crop of hay cutting that have grown the most thermophilic actinomycetes.

Little is known about the prevalence of farmer's lung in the agricultural areas of the USA. Most of the cases have been reported in the Wisconsin area where climatic conditions favor the development of significant actinomycete growth during the storage of hay. Madsen et al. [32] studied 471 persons associated with farming or dairy production in Wisconsin. A history typical of farmer's lung syndrome was given by 14 of the 471 subjects (3.9%). Precipitins were positive in 2 of these 14 patients and spiograms were abnormal in 4. They concluded that farmer's lung may represent a frequent occupational illness of dairy and cattle workers in the USA who are exposed to stored hay or grain and that the prevalence of the disease approximated that found in England and Scotland.

In summary, the prevalence of farmer's lung appears to be related to heavy occupational exposure to contaminated hay in farmers in communities with climatologic conditions of heavy rain and humidity and it may be expected to be more frequent in males.

Humidifier Fever/Ventilation Pneumonitis

These conditions are related to exposure to contaminated warm residual water in humidifiers and contaminated water in certain air conditioners. Cases appear as reports of isolated outbreaks in buildings and specific industries but the prevalence of the disease has not been studied in the population at large. Banazak et al. [33] reported hypersensitivity pneumonitis in 15% of workers exposed to a contaminated air condition system in a large office building. In a study by Ganier et al. [34], symptoms of humidifier's lung occurred in 26 (52%) of 50 employees working in a localized area of a large factory. This area was the only unit in the entire factory which used a water filtration humidification unit. In a large stationery factory employing

560 workers in the production area near the maintenance shop, 15 out of 21 workers developed symptoms. Exposure was related to contaminated vacuum pumps [35].

In a study by Bernstein et al. [36], 2 of 14 employees of an office reported symptoms compatible with humidifier fever. It was demonstrated that the forced air-heater-cooler units were heavily contaminated with fungi, particularly penicillium species. Ashton et al. [37] reported studies in a group of office workers whose premises adjoined a factory manufacturing cellulose products. Contaminated steam from the factory entered the office. Forty-seven workers were exposed, 11 reported respiratory symptoms and 9 demonstrated decreases in FEV₁ following exposure to the environment. These figures suggest that the populations at risk are fairly high if there is a high degree of exposure in a closed environment.

Pigeon Breeder's Disease

There is little information regarding relationship between avian antigens and disease in exposed population. Hendrick et al. [38] reported an incidence of respiratory symptoms related to exposure to birds in 3.4% of 117 budgerigar owners. Elgefors et al. [39] detected avian-related respiratory symptoms in 8% of 180 pigeon breeders and Caldwell et al. [40] in 6% of 150 pigeon breeders. Fink et al. [41] reported that up to 40% of exposed but asymptomatic pigeon breeders had a detectable humoral and cellular immune response to pigeon antigens without clinical evidence of disease. The same investigators [19] evaluated 200 pigeon breeders attending a convention. There was a 40% incidence of precipitating antibodies to pigeon antigen; 16% had abnormal pulmonary function studies and 31% had respiratory symptoms with normal pulmonary function studies. These values are similar to those reported in several general population surveys. There was no correlation with symptoms or X-ray findings. No cases of pigeon breeder's disease were detected. On the other hand, studies by Christiansen et al. [42] of pigeon breeders' club members indicate that between 6 and 21% of exposed pigeon breeders have detectable disease. Thus, upon reviewing the literature it is difficult to obtain a clear picture regarding the prevalence of the disease in individuals with similar exposure. The reported number of patients with detectable disease ranges from 3 to 15%.

Maple Bark Disease

This disease was initially described by Towey et al. [43] in a group of bark peelers in northern Michigan and further studied by Emanuel et al. [44]

during an epidemic of the disease in a paper mill in northern Wisconsin. This type of hypersensitivity pneumonitis is caused by the inhalation of spores of *Cryptostroma corticale*, which is found growing beneath the bark of maple logs. Wenzel and Emanuel [45] performed an epidemiologic study of the disease in a paper mill in which an outbreak of hypersensitivity pneumonitis occurred. Thirty-seven workers were studied by clinical history, physical examination, chest X-ray and precipitin test. Five patients demonstrated active disease (13.5%), 9 additional individuals had findings suggestive of HP (24%), and a total of 9 individuals had positive precipitating antibodies to cryptostroma antigen. Preventive measures established in this mill, as well as throughout the lumber industry, have practically eliminated maple bark disease.

Bagassosis

This form of HP results from the inhalation of thermophilic actinomycete-contaminated sugar cane fiber (bagasse). Although a high percentage of the cases have been detected in Louisiana (USA), this disease has a worldwide distribution in areas where sugar cane is processed and bagasse is utilized in the manufacture of paper or cardboard (including several Caribbean countries, India, Italy, Peru and the Philippines) [46]. Major outbreaks of the disease have been reported by Buechner et al. [47] in a cardboard manufacturing plant in Vacherie. This plant began operations in 1962 utilizing baled dry bagasse as the raw material for the manufacture of boards. Within 2 years of operation an estimated 200 cases of bagassosis had occurred. In a paper mill in Puerto Rico using bagasse fiber in the manufacture of commercial paper, out of 140 exposed workers 69 (49%) had a clinical picture consistent with bagassosis [48]. Hearn [49] performed an epidemiologic and environmental survey of a group of 170 bagasse workers employed by a raw sugar producing company in Trinidad. During a 5-year period, 17 patients with bagassosis were seen in this factory. There was no significant increase in prevalence of respiratory symptoms in workers with heavy exposure to bagasse. More recently, we investigated the prevalence of the disease in a Louisiana paper mill which in the past had considerable numbers of workers with bagassosis [50]. Based on clinical history and serologic studies we concluded that bagassosis was no longer present. This was thought to be due to several factors, among which were a different method of storage of bagasse, which retards microbial decay and reduces airborne organic dust; an increased awareness resulting in greater safety measures; the maintenance of a very high water content of the stored material using a sprinkler system,

and the rapid use of the bagasse for manufacturing purposes with reduction in storage time.

Conclusion

There are numerous causes of hypersensitivity pneumonitis, the majority of etiologic agents being derived from occupational exposure, such as farming, sugar cane harvesting, and working with cereal grain or wood products. The disease may also result from nonoccupational or avocational factors, such as exposure to contaminated central heating and humidification systems.

The manner by which inhaled organic dusts induce hypersensitivity pneumonitis depends on a complex interrelationship between environmental, genetic, and other host-related factors. In addition to serving as potent sources of antigen, the organic dusts producing this condition exert a wide variety of nonspecific biologic effects, among which are their ability to act as immunologic adjuvants. The concentration of the etiologic agents in a given environment also varies significantly according to climatic, meteorologic and local conditions. These all affect the overall epidemiology of the disease process.

At present there is little information regarding the levels of exposure necessary to cause the disease in susceptible individuals. Although exposure to offending antigens is universal in some occupations and there is a high incidence of both precipitating antibodies against the offending antigens and lymphocytosis in exposed individuals on bronchoalveolar lavage cell analysis, the incidence of the disease appears to be low (less than 10% of exposed subjects). Furthermore, the factors that differentiate between symptomatic and asymptomatic exposed subjects are not clear.

In virtually all types of hypersensitivity pneumonitis studied, epidemiologic studies have revealed that precipitins against extracts of the appropriate offending antigen are present not only in symptomatic individuals but in over 50% of those who have been exposed but have not developed overt disease. Thus, serum precipitins seem to be a marker reflecting exposure to potential etiologic agents.

Epidemiologic studies of hypersensitivity pneumonitis are further complicated by the fact that it represents a group of syndromes rather than a single disease with a single etiologic agent. There is also lack of agreement regarding the diagnostic criteria needed for planning and carrying out

epidemiologic studies to determine disease prevalence in any given population. Some studies rely only on clinical symptoms as the basis for disease diagnosis; others attempt to use chest roentgenograms, biopsies, or inhalation challenge studies, which prove very impractical and cumbersome for large epidemiologic studies. These limitations obviously have prevented accurate data regarding the distribution and prevalence of certain types of hypersensitivity pneumonitis.

In the 5 types of hypersensitivity pneumonitis discussed in this article, we were able to uncover little definitive data regarding the true prevalence of these diseases, and it is likely that the actual published incidence may be underestimated due to difficulties in establishing diagnostic criteria. Studies in farmer's lung have shown that the prevalence varies from country to country and even within a country depending on local geographic and atmospheric conditions. In humidifier fever/ventilation pneumonitis, the available data suggest that the populations at risk are fairly high if there is a high degree of exposure and a relatively closed environment; in pigeon breeder's disease, it seems difficult to obtain a clear picture regarding the disease prevalence in individuals with similar exposure rates, but the reported number of patients with detectable diseases ranges from 3 to 15%; in maple bark disease it is of interest that preventive measures established throughout the lumber industry have virtually eliminated symptomatic episodes. Finally, in bagassosis up to 50% of exposed workers have been known to develop a clinical picture consistent with the disease when highly contaminated bagasse samples were used in 'dry' manufacturing processes. Yet other studies of the bagasse industry have shown that bagassosis can also be virtually eliminated if care is taken to change the methods of storage of the material and to retard microbial decay as well as use material rapidly for manufacturing purposes.

All of the above data indicate that given the appropriate occupational or avocational setting, the incidence of these diseases may be relatively high but with proper control measures many of the diseases can likely be prevented or even eliminated.

References

- 1 Pepys, J.: Hypersensitivity disease of lung due to fungi and other organic dusts. *Monogr. Allergy* 4: 44-50 (1969).
- 2 Schatz, M.; Patterson, R.: Hypersensitivity pneumonitis — general considerations. *Clin. Rev. Allergy* 1: 451-467 (1983).

- 3 Fink, J.: Hypersensitivity pneumonitis. *J. Allergy clin. Immunol.* 74: 1-9 (1984).
- 4 Salvaggio, J.E.; de Shazo, R.D.: Pathogenesis of hypersensitivity pneumonitis. *Chest* 89: 1905-1925 (1986).
- 5 Gregory, P.H.; Lacey, M.E.: Mycological examination of the dust from moldy hay associated with farmer's lung disease. *J. gen. Microbiol.* 30: 75-88 (1963).
- 6 Lacey, J.; Lacey, M.: Spore concentration in the air of farm buildings. *Trans. Br. Mycol. Soc.* 47: 547-552 (1964).
- 7 Bice, D.E.; McCarron, K.; Hoffman, E.O.; Salvaggio, J.: Adjuvant properties of *Micropolyspora faeni*. *Int. Archs Allergy appl. Immun.* 55: 267-274 (1977).
- 8 Stankus, R.P.; Cashner, F.M.; Salvaggio, J.E.: Bronchopulmonary macrophage activation in the pathogenesis of hypersensitivity pneumonitis. *J. Immun.* 120: 685-688 (1978).
- 9 Edwards, J.H.; Baker, J.T.; Davies, B.H.: Precipitin test negative farmer's lung. Activation of the alternative pathway of complement by moldy hay dust. *Clin. Allergy* 4: 379-388 (1974).
- 10 Schorlemmer, H.U.; Edwards, J.H.; Davies, P.; Allison, A.C.: Macrophage responses to moldy hay dust. *Micropolyspora faeni* and zymosan, activators of complement by the alternative pathway. *Clin. exp. Immunol.* 27: 198-207 (1977).
- 11 Rylander, R.; Hagling, P.; Landhult, M.; Mattsby, I.; Stengrist, I.: Humidifier fever and endotoxin exposure. *Clin. Allergy* 8: 511-516 (1978).
- 12 Burrell, R.; Polomey, H.: Mediators of experimental hypersensitivity pneumonitis. *Int. Archs Allergy appl. Immun.* 55: 161-169 (1977).
- 13 Rodey, G.E.; Fink, J.; Loethe, S.: A study of HLA-A, B, C, and DR specificities in pigeon breeder's disease. *Am. Rev. resp. Dis.* 119: 755-759 (1979).
- 14 Flaherty, D.K.; Braun, S.R.; Marx, J.J.; Blank, J.L.; Emanuel, D.A.; Rankin, J.: Serologically detectable HLA-A, B, and C loci antigens in farmer's lung disease. *Am. Rev. resp. Dis.* 122: 437-443 (1980).
- 15 Muers, M.F.; Faux, J.A.; Ting, A.; Morris, P.J.: HLA-A, B, C, and HLA-DR antigens in extrinsic allergic alveolitis (budgerigar fancier's lung disease). *Clin. Allergy* 12: 47-53 (1982).
- 16 Kawai, T.; Tamara, U.; Murao, M.: Summer-type hypersensitivity pneumonitis. A unique disease in Japan. *Chest* 85: 311-317 (1984).
- 17 Salvaggio, J.E.; Arquembourg, P.; Seabury, J.; Buechner, H.: Bagassosis. IV. Precipitins against extracts of thermophilic actinomycetes in patients with bagassosis. *Am. J. Med.* 46: 538-544 (1969).
- 18 Barboriak, J.J.; Sosman, A.J.; Reed, C.E.: Serological studies in pigeon breeder's disease. *J. Lab. clin. Med.* 65: 600-604 (1965).
- 19 Fink, J.N.; Schleiter, D.P.; Sosman, A.: Clinical survey of pigeon breeders. *Chest* 62: 277-281 (1972).
- 20 Chmelik, F.; Reed, C.E.: Precipitating antibodies in office workers and hospitalized patients directed toward antigens causing hypersensitivity pneumonitis. *Am. Rev. resp. Dis.* 111: 201-205 (1975).
- 21 Kawai, T.; Salvaggio, J.; Arquembourg, P.; Marsh, D.: Precipitating antibodies against organic dust antigen in human sera by counterimmunoelectrophoresis. *Chest* 64: 420-426 (1973).
- 22 Pepys, J.; Jenkins, P.A.: Precipitins (F.I.H.) test in farmer's lung. *Thorax* 20: 21-35 (1965).
- 23 Roberts, R.C.; Wenzel, F.J.; Emanuel, D.S.: Precipitating antibodies in a midwest

- dairy farming population toward the antigens associated with farmer's lung disease. *J. Allergy clin. Immunol.* 57: 518-524 (1976).
- 24 Gump, D.W.; Bobbott, F.F.; Holly, C.; Sylvester, D.L.: Farmer's lung disease in Vermont. *Respiration* 37: 52-60 (1979).
 - 25 Solal-Celigny, P.H.; Laviolette, M.; Herbert, J.; Cormier, Y.: Immune reactions in the lungs of asymptomatic dairy farmers. *Am. Rev. resp. Dis.* 126: 964-967 (1984).
 - 26 Grant, I.W.; Blyth, W.; Wardrop, V.E.; Gordon, R.M.; Pearson, J.C.G.; Mair, A.: A prevalence of farmer's lung in Scotland. A pilot survey. *Br. med. J. i*: 530-534 (1972).
 - 27 Staines, F.H.; Forhman, J.A.D.: A survey of farmer's lung. *J.R. Coll. Gen. Pract.* 4: 351-382 (1961).
 - 28 Heinonem, P.O.; Husman, K.; Terho, E.O.; Vohlonen, I.: Farmer's lung, asthma and chronic bronchitis in the Finnish farming population with respect to atopy, smoking and precipitating antibodies. *Eur. J. resp. Dis.* 63: suppl., pp. 124-138 (1982).
 - 29 Mastrangelo, G.; Reggio, O.; Zambon, P.; Saia, B.: Screening delle bronchopneumonie in agricoltura aspetti epidemiologici ed ambientali. Cremona 16-17 Gennaio 43-51 (1981).
 - 30 Shelley, E.; Dean, G.; Collins, D.; et al.: Farmer's lung. A study in North-West Ireland. *J. Irish med. Ass.* 72: 261-264 (1979).
 - 31 Emanuel, D.A.; Kryda, M.J.: Farmer's lung disease. *Clin. Rev. Allergy* 1: 509-532 (1983).
 - 32 Madsen, D.; Kloch, L.E.; Wenzel, F.J.; LaMar, J.; Schmidt, C.D.: The prevalence of farmer's lung in an agricultural population. *Am. Rev. resp. Dis.* 113: 171-174 (1976).
 - 33 Banazak, E.F.; Thiede, W.H.; Fink, J.N.: Hypersensitivity pneumonitis due to contamination of air conditioner. *New Engl. J. Med.* 283: 271-276 (1970).
 - 34 Ganier, M.; Lieberman, P.; Fink, J.; Lockwood, D.G.: Humidifier lung. An outbreak in office workers. *Chest* 77: 183-187 (1980).
 - 35 Friend, J.A.R.; Gaddie, J.; Palmer, K.N.V.; Pickering, C.A.C.; Pepys, J.: Extrinsic allergic alveolitis and contaminated cooling water in a factory machine. *Lancet* i: 297-300 (1977).
 - 36 Bernstein, R.S.; Sorenson, W.G.; Garabrant, D.; Reaux, C.H.; Treitman, R.D.: Exposures to respirable airborne penicillium from a contaminated ventilation system. Clinical environmental and epidemiological aspects. *Am. Ind. Hyg. Ass. J.* 44: 161-169 (1983).
 - 37 Ashton, I.; Axford, A.T.; Bevan, C.; Cotes, J.E.: Lung function of office workers exposed to humidifiers fever antigen. *Br. J. intern. Med.* 38: 34-37 (1981).
 - 38 Hendrick, D.J.; Faux, J.A.; Marshall, R.: Budgerigar fancier's lung. The commonest variety of allergic alveolitis in Britain. *Br. med. J. ii*: 81-84 (1978).
 - 39 Elgefors, B.; Belin, L.; Hanson, L.B.: Pigeon breeder's lung. Clinical and immunological observations. *Scand. J. resp. Dis.* 52: 167-176 (1971).
 - 40 Caldwell, J.R.; Pearce, D.E.; Spencer, C.; Leder, R.; Waldman, R.H.: Immunological mechanisms in hypersensitivity pneumonitis. *J. Allergy clin. Immunol.* 52: 225-230 (1973).
 - 41 Fink, J.N.; Barboriak, J.J.; Sosman, A.J.; Bukosky, R.J.; Arkins, J.A.: Antibodies against pigeon serum proteins in pigeon breeders. *J. Lab. clin. Med.* 71: 20-24 (1968).
 - 42 Christensen, L.T.; Schmidt, C.D.; Robbins, L.: Pigeon breeder's disease. A prevalence study and review. *Clin. Allergy* 5: 417-430 (1975).
 - 43 Towey, J.W.; Sweany, H.C.; Huron, W.H.: Severe bronchial asthma apparently due to fungus spores found in maple bark. *J. Am. med. Ass.* 99: 453-459 (1932).

- 44 Emanuel, D.A.; Wenzel, F.J.; Lawton, B.R.: Pneumonitis due to *Cryptosporidia* (maple bark disease). *New Engl. J. Med.* 274: 1413-1418 (1966).
- 45 Wenzel, F.J.; Emanuel, D.A.: The epidemiology of maple bark disease. *Archs envir. Hlth* 14: 385-389 (1967).
- 46 Bucchner, H.A.: Bagassosis peculiarities of its geographical pattern and report of the first case from Peru and Puerto Rico. *J. Am. med. Ass.* 174: 1237-1241 (1960).
- 47 Bucchner, H.A.; Aucoin, E.; Vignes, A.J.; Weill, H.: The resurgence of bagassosis in Louisiana. *J. occup. Med.* 6: 437-442 (1964).
- 48 Bayonet, N.; Lavergne, R.: Respiratory disease of bagasse workers. A clinical analysis of 69 cases. *Industr. med. Surg.* 25: 519-522 (1960).
- 49 Hearn, C.E.D.: Bagassosis. An epidemiological, environmental and clinical survey. *Br. J. intern. Med.* 25: 267-282 (1968).
- 50 Lehrer, S.B.; Turer, E.; Weill, H.; Salvaggio, J.E.: Elimination of bagassosis in Louisiana paper manufacturing plant workers. *Clin. Allergy* 8: 15-20 (1978).

Prof. Dr. Manuel Lopez, Director Clinical Immunology Laboratories,
Tulane University, School of Medicine, Suite 7209, 1430 Tulane Avenue,
New Orleans, LA 70112 (USA)

apuyen

FAIT CLINIQUE

Manifestations respiratoires avec présence de précipitines au charençon de blé (*)

par

J. SAUVAGET ⁽¹⁾, J. AERTS ⁽¹⁾, J.-C. GACOUIN ⁽¹⁾,
F. REYBOZ ⁽²⁾, J. LORIOT ⁽²⁾ et J. PROTEAU ⁽²⁾.

⁽¹⁾ Service de pneumologie et allergologie de l'Hôpital de Saint-Joseph, 7, rue Pierre-Larousse, 75014 Paris.
⁽²⁾ Chaire de médecine du travail, Faculté de médecine, Broussais-Hôtel-Dieu.

SUMMARY. Respiratory manifestations, with presence of precipitins, due to wheat weevil.

Wheat weevil or Sitophilus granarius can produce reaginic allergic manifestations, or, more seldom, troubles of belated hypersensitivity.

The authors report two clinical observations concerning workers occupationally exposed, with evidence of specific precipitins, the interpretation of which is discussed.

The systematic search of these precipitins in exposed environment seems to be advisable in the future.

RÉSUMÉ. Le charençon du blé ou *Sitophilus granarius* peut entraîner des manifestations allergiques réagéniques, ou plus rarement des troubles d'hypersensibilité retardée.

Les auteurs rapportent deux observations cliniques concernant des sujets professionnellement exposés, avec mise en évidence des précipitines spécifiques, dont ils discutent l'interprétation.

La recherche systématique de ces précipitines en milieu exposé paraît être conseillée dans l'avenir.

Le 66^e tableau de maladies professionnelles, récemment publié par le décret du 2 juin 1977 (J.O. du 19 juin 1977), concerne les affections respiratoires professionnelles de mécanisme allergique.

Les manifestations allergiques réagéniques apparaissent comme fréquentes et bien connues chez les boulangers et les minotiers ; par contre, les troubles liés à une hypersensibilité de type semi-retardé sont plus rarement décrits.

Celle-ci se caractérise par la présence dans le sérum d'anticorps précipitants, et dans

(*) Communication présentée devant la Société de médecine et d'hygiène du travail lors de sa séance du 13 mars 1978.

Mots-clés : charençon du blé ; pneumopathies allergiques à précipitines ; maladie professionnelle.

Tirés à part : J. SAUVAGET, à l'adresse ci-dessus.

cette catégorie professionnelle l'antigène capable d'induire la formation de ces précipitines peut être un insecte : le charençon du blé ou *Sitophilus granarius*, qui appartient à l'ordre des coléoptères, de la famille des *curculionidae*, et mesure 3 mm de long. Il se caractérise par une trompe allongée sur le devant de la tête, au sommet de laquelle se trouvent les pièces buccales.

Il parasite toutes sortes de grains, principalement le blé, mais aussi le maïs et le riz ainsi que leurs farines.

Le charençon est à l'origine d'allergie de type I sous forme de réactions asthmatiformes, mais aussi d'allergie de type III, entraînant des alvéolites allergiques extrinsèques.

Il nous a paru intéressant de rapporter ici deux cas de sujets professionnellement exposés, atteints d'affections respiratoires très différentes, mais chez lesquels ont été mises en évidence des précipitines spécifiques.

Les discussions sur l'aspect clinique et l'interprétation de la présence de ces précipitines illustrent de façon concrète les problèmes posés par la parution de ce nouveau tableau.

Ces deux cas ont été observés récemment dans le service de pneumo-physiologie de l'un de nous, à l'hôpital Saint-Joseph à Paris.

Observations.

Cas. I. — M. L., âgé de 56 ans, est hospitalisé dans le service le 15 janvier 1976 pour une poussée d'insuffisance respiratoire aiguë.

Dans ses antécédents, on note une intoxication alcool-tabagique chronique, aucun élément allergique, mais surtout le malade exerce la profession de boulanger depuis l'âge de 14 ans jusqu'à l'âge de 53 ans, où son insuffisance respiratoire l'oblige à restreindre puis à cesser toute activité.

L'histoire de la maladie débute brutalement durant l'hiver 1972-1973 par un épisode bronchitique fébrile associé à une dyspnée, régressant lentement.

Les mêmes accès se répètent chaque hiver, aggravant progressivement la dyspnée qui devient permanente.

En 1975, il est hospitalisé en cardiologie pour une poussée d'insuffisance cardio-respiratoire, traitée par tonocardiaques et diurétiques. Un cathétérisme droit conclut à une insuffisance cardiaque avec hypertension artérielle pulmonaire précapillaire.

A son entrée dans le service, le malade est fébrile (39°) ; la toux ramène une expectoration muco-purulente ; la dyspnée est importante et permanente.

L'auscultation pulmonaire retrouve des râles sibilants bilatéraux ; les bruits du cœur sont assourdis et rapides (100/mn) ; la T.A. est normale (13/8).

On retrouve enfin des signes de défaillance cardiaque droite (galop droit, hépatomégalie avec reflux hépato-jugulaire, œdèmes périphériques).

La radiographie thoracique objective une cardiomégalie associée à une hyperclarté des bases et à une distension thoracique.

A l'E.C.G., il existe une tachycardie sinusale associée à des signes de cœur pulmonaire chronique.

Le bilan biologique est normal en dehors d'une V.S. à 45/75 et d'une hyper-alpha-2-globulinémie (13 % pour 62g/l de protéides).

Par contre les gaz du sang pratiqués à l'admission du malade objectivent : PCO_2 : 43 mm Hg ; PO_2 : 40 mm Hg ; pH : 7,4 ; BE : + 4.

On est frappé par l'existence d'une hypoxie majeure, alors que l'hypercapnie reste modérée.

Les examens de crachats montrent la présence de *Proteus* ; la recherche de BK est négative.

MANIFESTATIONS RESPIRATOIRES DUES AU CHARENÇON DU BLÉ 619

Le malade est alors traité par antibiotiques, corticoïdes, anticoagulants, diurétiques, kinésithérapie respiratoire et oxygénothérapie, qui entraînent une amélioration lente en une quinzaine de jours.

L'exploration fonctionnelle respiratoire objective les valeurs suivantes : CV = 2,460 l (-42,5 %), VEMS = 0,570 l (-82 %), Tiffeneau = 23 %, VR = 1,600 l, CT = 4,060 l, VR/CT = 39,5 %, temps de mixique = 3,5 mn, DCO = 8 cc mn mmHg.

Un bilan étiologique est pratiqué. Compte tenu de la profession du sujet et de la rapidité de l'évolution, malgré un syndrome obstructif grave, les explorations sont poursuivies afin de rechercher une éventuelle alvéolite allergique. Une biopsie pulmonaire par voie transbronchique révèle l'existence d'une fibrose interstitielle diffuse.

Enfin, une recherche de précipitines est adressée au Dr Walbaum (INSERM de Lille) qui utilise la technique d'Ouchterlony. Les résultats sont les suivants :

Sitophilus granarius : 2 arcs
Thermoactinomyces vulgaris : 0
Thermomonospora viridis : 0
Micro-polyspora faeni : 0
Aspergillus fumigatus : 0

M. L... quitte le service le 26 février 1976 sans avoir été amélioré par un traitement corticoïde. L'évolution se fait vers une aggravation progressive, et le 3 septembre 1976 il est admis en réanimation pour une nouvelle poussée d'insuffisance respiratoire aiguë. Le 24 septembre 1976, il décède après un coma de quelques jours. Aucune vérification anatomique n'a malheureusement pu être faite.

Obs. 2. — M. S..., âgé de 29 ans, est hospitalisé le 30 avril 1976 pour une toux persistant depuis 2 mois.

Comme antécédent, on ne note aucun élément allergique, aucune affection respiratoire : absence de tabagisme. Mais le sujet travaille depuis 10 ans comme ensacheur dans une minoterie industrielle.

Le tableau clinique évoque d'emblée une trachéite spasmodique allergique : toux quinteuse apparue depuis 2 mois, survenant sur les lieux de travail et durant toute la journée pour tendre à disparaître durant les week-ends ou les arrêts de travail, s'accompagnant de râles sibilants.

A l'entrée dans le service, le malade présente une fébricule à 37°8, une petite toux ramenant une expectoration minime, blanchâtre. L'examen clinique est totalement normal, de même que la radiographie de thorax et l'ensemble du bilan biologique. L'évolution spontanée est satisfaisante, puisque le patient est soustrait à un éventuel allergène. Un bilan est alors entrepris.

L'exploration fonctionnelle respiratoire est strictement normale, y compris la DLCO.

Sur le plan allergologique, des tests cutanés mettent en évidence une allergie à la farine et à la poussière de maison, et une désensibilisation est entreprise.

Une recherche de précipitines est pratiquée dans les mêmes conditions que précédemment, montrant :

<i>Sitophilus granarius</i> :	3 arcs de précipitation
<i>Aspergillus fumigatus</i> :	1 arc
fientes de pigeon :	1 arc
sérum de pigeon :	0
sérum de perruches :	0
fientes de perruches :	0
<i>Micropolyspora faeni</i> :	0
<i>Thermoactinomyces vulgaris</i> :	0
<i>Thermomonospora viridis</i> :	0

Le malade quitte le service le 21 mai 1976 en poursuivant sa désensibilisation, et on conseille à son entreprise un changement de poste.

Gells et Coombs ont classé les réactions immuno-allergiques en 4 types fondamentaux.

Les réactions de type I ou réactions anaphylactiques recouvrent les phénomènes d'allergie immédiate d'origine humorale. Les anticorps, appelés réagins, appartiennent aux immunoglobulines E (IgE) et sont dits cytophiles, car ils se fixent sur la membrane de certaines cellules : basophiles dans le sang et mastocytes dans les tissus. Ces cellules contiennent des granulations chargées en histamine et autres amines vaso-actives. L'anticorps étant fixé sur la membrane cellulaire, l'antigène va se combiner avec lui et entraîner la libération de granulations cytoplasmiques et, par conséquent, celle de divers produits responsables des manifestations pathologiques.

En pathologie, les réactions de type I sont responsables du choc anaphylactique, des phénomènes d'anaphylaxie locale et surtout des maladies dites *atopiques* parmi lesquelles se placent l'œdème de Quincke, l'urticaire, les rhinites allergiques et surtout l'asthme. En pratique courante, le diagnostic de cette allergie repose sur des critères cliniques et la pratique de tests cutanés qui, lorsqu'ils sont positifs, vont donner une réaction précoce, d'où le terme d'allergie immédiate.

Dans les réactions de type II ou réactions cytotoxiques, l'antigène, fixé à la membrane cellulaire, réagit avec l'anticorps, et si le complexe formé fixe le complément, la réaction peut aboutir à une cytolysse.

Ce type de réaction est observé dans la maladie hémolytique du nouveau-né, les accidents de transfusion, le syndrome de Goodpasture...

Les réactions de type III ou réactions à immuns complexes. L'hypersensibilité de type semi-retardé s'exprime par des réactions dues à la formation de complexes antigène-anticorps dans le sérum, capables de précipiter, d'où le nom d'anticorps précipitants de ces anticorps de type IgG.

Ces complexes précipitent dans les parois vasculaires en fixent le complément et deviennent alors histo-toxiques. En effet, l'activation du complément s'accompagne de la libération d'un facteur chimiotactique qui attire des neutrophiles et va aboutir à la libération d'anaphylatoxines engendrant une forte réaction inflammatoire.

De très nombreux antigènes sont susceptibles de déterminer l'apparition de précipitines et d'être à l'origine des manifestations pathologiques cliniques : maladie sérique, glomérulonéphrite poststreptococcique, vascularite allergique et surtout granulomatoses pulmonaires allergiques extrinsèques.

En pratique, la recherche des précipitines utilise l'immunodiffusion selon la méthode d'Ouchterlony, ainsi que l'immunoélectrophorèse.

Les réactions de type IV (allergie à médiation cellulaire) représentent l'allergie de type retardé, dont le meilleur exemple est l'hypersensibilité tuberculinique.

Ce type de réaction est dit d'origine cellulaire, car il ne fait pas intervenir les anticorps circulants et n'est donc pas transmissible par le sérum et repose sur l'intervention des lymphocytes T.

Elle intervient dans plusieurs phénomènes, outre l'allergie tuberculinique : les dermatoses allergiques de contact, le rejet des greffes, la défense contre certaines bactéries ou virus, certaines maladies auto-immunes.

Commentaires.

Les affections respiratoires chez les travailleurs de la farine sont connues de longue date, puisqu'on doit à Ramazzini en 1713 la première description d'une maladie des « mesureurs et sasseurs » de grains, se traduisant par une toux, une dyspnée et une fièvre [13].

Plus près de nous, Wittich, puis Jimenez-Diaz et coll. [15], décrivent des cas d'asthme allergique lié aux céréales infestées de parasites.

De nombreuses enquêtes témoignent de la multiplicité des allergènes : farines diverses, *grain mill dust* qui est une poussière mixte des minoteries. Marchand souligne le rôle de certains produits chimiques employés comme agents de blanchiment [9]. Charpin note le rôle, quoique non exclusif, de certains parasites [3]. Cabanieu étudie l'allergie à *Ephestia*, capable d'induire également la formation de précipitines [2].

La mise en évidence du pouvoir antigénique du charençon du blé est due à Frankland et Lunn [7, 8] qui décrivent en 1965 les premières observations d'asthme chez deux laborantines manipulant *Sitophilus granarius*. En 1967, Lunn objective chez une de ces patientes des réactions allergiques de type III avec des réponses semi-retardées à des tests cutanés et d'inhalation utilisant un extrait à 1 % de *sitophilus*. Une recherche de précipitines anti-*sitophilus* est positive [8].

Ainsi est révélée la dualité des réponses allergiques vis-à-vis du charençon : réactions asthmatiformes par hypersensibilité immédiate et réactions semi-retardées de type III.

Peu de cas de pneumopathies à précipitines sont cependant rapportés dans la littérature. A notre connaissance, seule S. Storage-Piquet, dans sa thèse de 1973, rapporte un cas de granulomatose allergique au charençon du blé, assez caractéristique et ayant régressé sous traitement corticoïde [14].

Les observations que nous rapportons mettent en évidence des précipitines spécifiques chez des travailleurs exposés, mais leur rôle pathogénique peut être discuté.

DANS LE PREMIER CAS :

Il s'agit avant tout d'un tableau de bronchopneumopathie chronique avec syndrome obstructif majeur, dominant le pronostic. Cet élément peut suffire à expliquer les troubles de la diffusion des gaz. De même, les résultats de la biopsie pulmonaire sont difficilement interprétables dans ce contexte et par cette technique (taille minime des éléments biopsiés).

Cependant, l'intervention de facteurs allergiques ne peut être éliminée, même si l'aspect radiologique n'est pas évocateur de granulomatose.

Sur le plan clinique, on est frappé par le mode de début brutal, évoluant par poussées hivernales successives, avec aggravation très (pour ne pas dire trop) rapide. Il existe d'autre part un syndrome restrictif, même s'il passe au second plan ; les gaz du sang évoquent un bloc alvéolo-capillaire concordant avec les données anatomiques. Enfin, sur le plan immunologique, l'existence de 2 arcs de précipitation vis-à-vis de *Sitophilus granarius* est remarquable si l'on se souvient que notre patient avait cessé toute activité professionnelle depuis environ 3 ans, car il est connu que le nombre d'arcs diminue progressivement avec la cessation de l'exposition.

DANS LE SECOND CAS :

Nous sommes en présence de deux types de réactions allergiques : hypersensibilité de type I avec équivalent d'asthme et tests cutanés positifs, hypersensibilité de type III avec présence de précipitines. Le nombre d'arcs est notable et témoigne, non seulement d'une exposition prolongée (10 ans), mais aussi d'une infestation certainement importante.

On ne peut malheureusement aller plus avant dans les conclusions. Faute d'extraits

de *Sitophilus*, il n'a pas été possible de pratiquer des tests cutanés et des tests d'inhalation à cet antigène, ce qui aurait permis d'affirmer ou d'infirmier un *asthme à précipitines*.

Il est donc impossible d'apprécier la valeur pathogénique de ces anticorps. Ne sont-ils qu'un témoin ? ou bien interviennent-ils dans la gravité de l'affection comme Molina l'indique à propos des asthmes à précipitines ? [11].

Dans ce cas précis, l'évolution a été satisfaisante dans l'immédiat, mais faute de recul on ne peut connaître le devenir de la maladie : reprise ou non des phénomènes spasmodiques, apparition à bas bruit d'une alvéolite, ou bien guérison totale ?

Conclusions.

Les 2 observations que nous venons de décrire mettent en lumière les difficultés d'interprétation soulevées par la découverte de précipitines dans des affections respiratoires très différentes.

Nous avons voulu essentiellement rappeler le rôle méconnu du charençon du blé en pathologie broncho-pulmonaire chez des sujets exposés. Cette méconnaissance rend difficile l'interprétation de son incidence en milieu professionnel. Cependant, en l'espace de quelques mois, chez 3 sujets travaillant en contact avec la farine, les précipitines ont été mises en évidence chez deux d'entre eux (ceux que nous rapportons) ; quant au 3^e, il avait exercé le métier de minotier il y a une dizaine d'années et seulement pendant un an ; il est donc logique de ne pas avoir découvert chez lui les anticorps spécifiques.

Dans une enquête de 1966, Lunn note 57 % de réactions cutanées positives au charençon chez des minotiers et 34 % dans une population témoin, ce qui témoigne d'une infestation importante, même si l'incidence pathologique est faible.

La découverte de précipitines, elle-même, n'a pas de signification clinique si elle est isolée. Ainsi, pour *Ephestia*, un autre parasite de la farine, des précipitines ont été mises en évidence chez 40 % de sujets sains, ce qui est un taux comparable à celui observé avec des antigènes aviaires.

Il serait donc intéressant de rechercher systématiquement les précipitines anti-*sitophilus* chez les sujets exposés professionnellement ; mais nous avons pu constater que la rareté des laboratoires possédant l'antigène rend une telle étude difficile ; de même, le manque de disponibilité de l'antigène empêche actuellement de pratiquer des tests de provocation et des test cutanés.

Seules de telles études permettraient d'apprécier l'importance de la maladie en milieu professionnel et d'engager des mesures préventives, même si elles s'avèrent délicates, voire de l'inscrire à un tableau de réparation de maladie professionnelle.

Sur le plan de la médecine du travail, un certain nombre de problèmes se posent.

Le délai de prise en charge : le tableau 66 l'a fixé à un an ; or, si le cas n° 2 est simple, puisque le malade était employé dans une minoterie lors de ses premiers troubles, il n'en va pas de même pour le cas n° 1, où le diagnostic précis de pneumopathie à précipitines n'a été porté que 3 ans après la fin de l'exposition au risque ; une telle situation est susceptible de donner lieu à des litiges.

A l'embauchage dans des entreprises à risque important, on devrait éliminer un certain nombre de sujets, *a priori* plus fragiles sur le plan broncho-pulmonaire :

insuffisants respiratoires, anciens tuberculeux, allergiques, bronchitiques chroniques, tabagiques.

La surveillance médicale devra être celle de tout travailleur, avec une particulière attention pour ceux qui présentent une quelconque symptomatologie respiratoire, qu'elle soit de type aigu ou chronique. Le rythme des examens pourrait être accéléré et le médecin du travail ne devra pas oublier la possibilité de demander des examens complémentaires spécifiques.

Mais ceux-ci sont, nous l'avons vu, difficiles à pratiquer dans les conditions actuelles. Ils sont par ailleurs coûteux et à la charge d'entreprises parfois modestes car artisanales, et ne peuvent entrer pour ces raisons dans le cadre d'une surveillance systématique.

Enfin, le problème de l'aptitude est particulièrement difficile à résoudre. Il est impensable de déclarer inapte un travailleur en état à peu près satisfaisant sur la seule présence de précipitines (nous avons vu que celles-ci existent dans une proportion importante des populations témoins).

Par contre, chez un travailleur exposé présentant à la fois des signes cliniques et biologiques d'alvéolite allergique, on se souviendra que ces lésions sont irréversibles et entraînent un avenir cardio-respiratoire médiocre, et on saura soustraire le malade à temps de son environnement pathogène.

Bibliographie

- [1] AERTS J. : A propos de deux cas d'affections respiratoires avec présence de précipitines au charençon du blé. *Thèse médecine*, Paris VI, 1977.
- [2] CARANIEU G. et BEZIAN J.-M. : Recherche des anticorps précipitants dans l'allergie à *Ephesia kuehniella*. *Revue fr. allergie*, 1971, 11, n° 3, 257.
- [3] CHARPIN et coll. : Étude allergologique chez les travailleurs de la farine. *Rev. fr. allergie*, 1964, 4, 2, 69.
- [4] DECROIX G. : La maladie des éleveurs d'oiseaux. *IX^e Journées nationales d'allergie*. Société Française d'Allergologie, Clermont-Ferrand, 5-7 juin 1970.
- [5] FRANKLAND A.-W. et LUNN J.-A. : Asthma caused by the grain weevil. *Erit. J. industr. med.* 1965, 22, 157.
- [6] JIMENEZ-DIAZ, LAMÓZ et CANTO : The allergens of mill dust. Asthma in millers, farmers and others. *Ann. allergy* 1947, 5, 519.
- [7] LUNN J. A. : Millworker's asthma. Allergic responses to the grain weevil. *Brit. J. industr. med.* 1966, 23, 149.
- [8] LUNN J. A. and HUGUES DTD : Pulmonary hypersensitivity to the grain weevil. *Brit. J. industr. med.* 1967, 24, 158.
- [9] MARCHAND M. : Pneumopathies par poussières végétales. *Rev. prat.*, 1958, 8, 1493.
- [10] MOLINA CL. : Immunopathologie broncho-pulmonaire. 1 vol., Masson, édit., Paris, 1973.
- [11] MOLINA CL., AIACHE J. M. et CHEMINAT J. C. : Diagnostic immunologique des pneumopathies professionnelles d'origine végétale. *Poumon et cœur*, 1968, 24, n° 3, 319.
- [12] PEPPYS J. : Hypersensitivity reactions in man to fung vegetable dusts and tuberculin. *Guy's Hosp. rep.*, 163, 2, 607.
- [13] RAMAZZINI B. : De morbus artificum diatriba, 1713 traduit par Walmer Cave Wright (1940), University of Chicago Press.
- [14] STORCKE-POUET S. : Un cas de granulomatosse allergique au charençon du blé. *Thèse médecine*, Paris V, 1973.
- [15] WRIGHT F.W. : *Lancet* 1940, 60, 418.

N.B. Cette bibliographie n'étant pas exhaustive, on pourra se reporter à celle de la thèse de J. Aerts [1].

Maladie des poumons des fermiers

par Guy Thony, M.D.
Chef du service médical
CLSC Jardin du Québec

Cette maladie fait partie des maladies pulmonaires par hypersensibilité. C'est le prototype de l'alvéolite allergique extrinsèque.

Elle résulte de l'inhalation de matières organiques provenant du foin moisi ou de matières végétales similaires (grains, blés, tabac, etc.).

Le foin moisi facilite la croissance rapide de fungus et de bactéries dans l'environnement. Il est riche en actinomycètes thermophiles (*Micropolyspora faeni* et *Micromonospora vulgaris*). La croissance des actinomycètes est favorisée par la fermentation et par la chaleur qui se dégage durant le processus de moisissure. Les actinomycètes thermophiles prédominent et le foin peut contenir plus de 10^9 spores d'actinomycètes par gramme.

On trouve des anticorps sériques précipitants contre le foin moisi ou contre les extraits

de *Micropolyspora faeni* et *Thermoactinomycètes vulgaris* chez 90 % des personnes atteintes de cette maladie. Cependant l'antigène le plus fréquent est dérivé de spores de *M. faeni*.

On peut reproduire les symptômes chez les patients atteints en leur faisant inhaler en aérosol un extrait de *M. faeni*. De plus, même si l'anticorps est démontré chez un nombre significatif de sujets exposés, très peu développeront la maladie quand ils sont placés dans un environnement pollué. On pense donc que la réponse immune serait en rapport avec une prédisposition génétique.

Enfin il semble que les états aigus et chroniques de la maladie dépendraient de la quantité d'antigènes inhalés et de la durée de l'exposition.

PATHOLOGIE

L'histopathologie dépend du temps écoulé entre l'exposition à l'antigène et l'examen des tissus.

1. LA FORME AIGÜE

La forme aiguë est caractérisée par les lésions suivantes:

- des nodules miliaires composés de cellules proliférantes avec lymphocytes, cellules plasmatiques, quelques neutrophiles et éosinophiles;
- les alvéoles présentent une paroi épaissie avec infiltration mononucléaire;
- une vasculite aiguë affecte les capillaires alvéolaires;
- une bronchiolite centro-lobulaire.

Il y a donc évidence histologique d'alvéolite, de réaction intersticielle, de bronchiolite et de vasculite. Par conséquent, le terme de pneumonite par hypersensibilité décrit bien ce syndrome.

2. LA FORME CHRONIQUE

La forme chronique est caractérisée par:

- une bronchiolite granulomateuse oblitérante;
- une fibrose intersticielle.

IMMUNOLOGIE

La présence d'anticorps circulant dans plusieurs cas de poumons des fermiers et l'apparition des symptômes, quatre à six heures après exposition, sont une forte évidence de l'implication de dépôt de complexe immun dans cette maladie.

Bien que des anticorps antinucléaires et antiglobulines aient été mis en évidence chez les personnes atteintes, il est peu probable qu'ils jouent un rôle direct dans la maladie.

Cependant, le rôle pathogénique du complexe immun dans la pneumonie par hypersensibilité n'est pas clair. En effet, on trouve surtout des anticorps circulants de la classe IgG, mais aussi des IgM et des IgA, à des taux similaires chez les fermiers symptomatiques et asymptomatiques. Ces mêmes anticorps se retrouvent chez les éleveurs de pigeons.

CLINIQUE

L'inhalation d'antigène sur une période de six à dix semaines a pour conséquence de sensibiliser la population exposée. Cependant, toute la population exposée ne développe pas la maladie après réexposition à l'antigène. L'apparition de la maladie semble dépendre de facteurs inconnus qui existent chez un nombre limité d'individus sensibilisés.

Il existe deux formes de la maladie: la forme aiguë et la forme chronique.

1. LA FORME AIGUË

La forme aiguë se développe de quatre à six heures après exposition à l'antigène: malaise, frissons, fièvre, nausée, toux sèche, dyspnée sans «wheezing».

Ces symptômes disparaissent spontanément dans quelques heures ou quelques jours.

L'examen physique peut révéler:

- ▷ cyanose,
- ▷ tachypnée,
- ▷ tachycardie,
- ▷ crépitants fins aux bases.

Laboratoire:

- ✓ leucocytose avec déviation vers la gauche;
- ✓ éosinophilie rare;
- ✓ pO_2 normal ou diminué;
- ✓ les anticorps précipitants contre le foin moisi sont trouvés à titre élevé dans le sérum. Cependant, ces anticorps traduisent une immunisation consécutive à des expositions antérieures et ne sont pas spécifiques à l'état de maladie.

Radiographie:

- la radiographie pulmonaire ne permet pas un diagnostic certain;

- cependant, on note de petites densités nodulaires multiples uniformément distribuées sauf aux apex et aux bases.

Exploration fonctionnelle:

- Réduction de la compliance.
- Réduction de la diffusion pulmonaire des gaz.
- Diminution de la capacité vitale forcée (FVC).
- Diminution du volume expiratoire forcé (FEV).
- Très peu de modification de rapport FEV/FVC.

2. LA FORME CHRONIQUE

La forme chronique est le résultat d'épisodes aigus répétés ou d'expositions continues ou répétées à l'antigène sans manifestations aiguës.

Cette forme est caractérisée par l'apparition insidieuse de symptômes respiratoires progressifs consécutifs à une fibrose pulmonaire.

- Les anticorps sont présents chez 50% des patients à des taux moins élevés que dans la forme aiguë.
- À la radiographie, on note des changements fibrotiques progressifs avec peu de densités nodulaires.
- Diminution du volume pulmonaire.

- Diminution de la capacité de diffusion.
- Diminution du FEV.
- Diminution du pO_2 .

La fibrose pulmonaire n'est pas réversible.

Traitement:

- Éviter exposition à l'antigène.

- Le cromoglycate disodique inhibe la réaction aiguë et mérite considération comme agent prophylactique.
- Les corticoïdes à haute dose sont efficaces en phase aiguë.

Dermatosen

8 - DERMATOSES

8.1 - Dermatitis irritatives

La dermatite irritative est une réaction inflammatoire localisée de la peau, non immunologique, caractérisée par de l'érythème, de l'œdème ou des abrasions suite à des traumatismes physiques répétés, constants ou à des applications répétées de substance sur un même site cutané.

Les points suivants sont à retenir :

- 1) toute substance, dans des circonstances appropriées, peut potentiellement causer une irritation de la peau
- 2) les dermatites irritatives de contact sont souvent le résultat d'expositions cumulatives à plusieurs irritants plutôt qu'à un seul
- 3) les dermatites irritatives restent confinées aux sites d'expositions, elles ne s'étendent pas.

On classe les dermatites irritatives selon 3 types :

Premier type : la dermatite est causée par une seule application d'une substance toxique (exemple : brûlure chimique avec le NaOH).

Deuxième type : la dermatite est causée par des applications répétées d'une substance qui, lors d'une seule exposition, ne causerait pas de réaction inflammatoire. La plupart des cas de dermatites irritatives se situent dans ce groupe (exemple : mains des ménagères, peau gercée, craquelée, fissurée, associé à des douleurs et des saignements).

Troisième type (s'il existe réellement) : dermatite irritative causée par des irritants faibles mais répétés comme dans le type deux, mais qui, à cause de facteurs constitutionnels inconnus, évoluent rapidement et présentent un aspect similaire aux dermatites de contact. Le diagnostic se fait par exclusion. Le test cutané est négatif.

Dans le domaine de l'alimentation, les dermatites irritatives sont surtout présentes chez les travailleurs exposés à des produits humides, les liquides biologiques, aux gestes répétitifs et au besoin de se laver fréquemment les mains. Il y a ici un cercle vicieux car l'exposition pendant le travail et le lavage nécessaire et fréquent des mains sont tous les deux des facteurs irritants.

A titre d'exemple, on trouve souvent des dermatites irritatives dans les milieux suivants : abattoir, boucherie, boulangerie, conserverie. De plus, dans ces milieux, le lavage fréquent des mains est nécessaire, d'où un assèchement avec perte de la protection naturelle des couches aqueuses et lipidiques cutanées.

Selon Hansen KS, le contact avec les protéines animales cause des dermatites dans les abattoirs. Les premiers signes sont la démangeaison suivi, dans les heures qui suivent, d'éruptions papulovésiculaires, principalement sur et entre les doigts. Cette maladie est décrite par les travailleurs comme "gut" ou "fat" eczéma. Il y aurait une prévalence de 22% chez ceux qui exercent et nettoient les intestins des animaux. La cause de cet eczéma demeure inconnu. Il n'y a pas encore d'explications toxicologiques ou immunologiques de ce phénomène. Pour se faire une idée de la distribution des lésions cutanées irritatives par rapport aux autres affections cutanées voir les statistiques pour un abattoir de poulet (tableau V).

Tableau V - Prévalence des dermatoses spécifiques chez les travailleurs des abattoirs

Symptom	Plant A		Plants B-D	
	Male	Female	Male	Female
Affected subjects	12	58	50	223
Maceration	5 (41.7)	26 (44.8)	26 (52.0)	112 (50.2)
Erosio interdigitalis	3 (25.0)	16 (27.6)	17 (34.0)	99 (44.4)
Pompholyx	2 (16.7)	2 (3.4)	11 (22.0)	13 (5.8)
Trichophytia unguium	1 (8.3)	10 (17.2)	3 (6.0)	11 (4.9)
Eczema	1 (8.3)	4 (6.9)	2 (4.0)	9 (4.0)
Others	0 (0)	3 (5.2)	3 (6.0)	9 (4.0)
Total no. dermatoses	12	75	69	297

Source : AM J Ind Med 15 : 601-605, 1989

Prévention

La protection personnelle demeure pratiquement le meilleur moyen pour éviter le mouillage constant des mains, principal agent causal des dermatites irritatives dans de nombreux champs d'activités alimentaires. Les gants doivent être souvent changés (5 à 6 fois/jour). L'incitation à la protection peut aussi se faire en fournissant des lieux de repos propres et sains avec lavabos et douches accueillantes. L'encouragement à la protection cutanée se conscientise souvent dans un climat favorable à la propreté.

Les gants imperméables peuvent être un problème pour ceux qui suent abondamment, causant ainsi de la macération. Les gants trop grands, trop petits sont à éviter. La supervision des dermatites est essentielle. Le traitement médical est efficace quand le travailleur n'est plus exposé ou se protège adéquatement.

8.2 - Dermatites de contact

8.2.1 Fruits et légumes

Les plantes culinaires sont les principales responsables des dermatites allergiques dans le domaine alimentaire. Le tableau VI illustre les principaux légumes et fruits allergènes par famille. Chez les employés de chaîne alimentaire ou épicerie on a relevé que le céleri était un offenseur fréquent dû à la présence de furanocoumarines.

Le contact avec la farine en particulier chez les boulangers peut causer des allergies de contact. La réaction est surtout due à la présence de persulfate d'ammonium qui agit comme libérateur d'histamine.

Les pesticides présents sur les fruits et les légumes peuvent causer en plus de l'irritation, des allergies de contact, de l'urticaire, de folliculites, des photodermites, des ulcérations, des changements pigmentaires, de l'érythème multiforme et des paralysies.

Les préservateurs comme le galate et le métrasulfite de sodium utilisés comme antioxydant pour différents légumes tels que choux-fleurs, patates de même que pour les viandes, volailles, poissons peuvent être allergisants.

Tableau VI - Plantes culinaires présentant un risque de dermatite de contact*

Family	Examples
Alliaceae	Onion, garlic clove, shallot
Bromeliaceae	Pineapple
Chenopodiaceae	Spinach
Compositae	Tarragon, artichoke, cardoon, chicory, chamomile, endive, lettuce
Cruciferae	Radish, horseradish, mustard, cabbage, sauerkraut, watercress, broccoli, brussels sprouts, cauliflower, capers
Cucurbitaceae	Cucumber, melon
Icacinaceae	Star anise
Labiatae	Basil, marjoram, oregano, rosemary, sage, savory, thyme, mint
Lauraceae	Bay laurel, cinnamon, cassia, sassafras
Leguminosae	Fenugreek
Myristiceae	Nutmeg, mace
Orchidaceae	Vanilla
Pedaliaceae	Sesame
Piperaceae	Pepper
Rutaceae	Apple, pear, orange, grapefruit, peach
Solanaceae	Paprika, cayenne, chili pepper, potato, tomato
Umbelliferae	Anise, caraway, celery, chervil, coriander, cumin, dill, fennel, parsley, carrot, lovage, parsnip
Zingiberaceae	Cardamon, ginger, turmeric
Miscellaneous	Alcohol, avocado, banana, beeswax, beetroot, food dyes, honey, hops, mango, molds, mushrooms, nuts, orange, lemon, pepper, rhubarb, sorbic acid, soybean, vermouth.

*Source : Mitchell JC, Rook A: Botanical Dermatology: Plants and Plant Products Injurious to the Skin. Philadelphia, Lea & Febiger, 1979.

Les dermatites de contact ne sont pas nécessairement plus fréquentes dans ce groupe, mais quand elles existent il faut regarder surtout les gants, le métal, les savons. Les écailles, la chair, ou les viscères de certains poissons peuvent causer des réactions d'urticaire de contact.

8.2.2 Prévention

La prévention se fait surtout par le biais de la protection personnelle et par la mécanisation des tâches, les deux prévenant des contacts allergisants. Souvent la relation de cause à effet avec le travail n'a pas été faite, aussi l'information joue-t-elle un rôle prépondérant dans ce genre de problème où les causes sont multiples. L'évaluation ou l'inventaire des risques dans l'environnement peut s'avérer laborieux, mais il est très utile.

8.3 - Dermatites infectieuses

8.3.1 Virus

Les individus qui travaillent avec du poisson frais ou congelé, la viande ou les volailles ont souvent des verrues. La cause des verrues ne serait pas l'alimentation mais le travail à l'humidité, au froid, et les protéines seraient un milieu favorable à la transmission d'un humain à l'autre. Les verrues apparaissent souvent dans les deux premières années de travail pour ne plus revenir même si un petit pourcentage de travailleurs en gardent très longtemps. La prévention demande qu'on les traite le plus tôt possible.

8.3.2 Infections fongiques

Les infections à *Candida Albicans* sont souvent présentes chez les travailleurs qui ont des contacts avec le sucre, les détergents et les fruits. Entre autres, les confectionneurs de confitures, les chefs cuisiniers et les pourvoyeurs. Comme pour la *Candida*, les infections à champignons sont favorisées par la noirceur et l'humidité, aussi en retrouve-t-on chez les travailleurs de la viande, de la volaille et du poisson.

Comme mesure préventive il convient de bien assécher la peau, utiliser des gants et se faire traiter tôt.

8.3.3 Infections bactériennes

Le staphylocoque est une des bactéries le plus souvent rencontré bien que toutes les autres se rencontrent aussi. Les blessures mineures, abrasions, piqûres, éraflures et le contact constant avec les protéines, les irritants et un milieu humide favorisent l'infection. On peut rechercher certaines infections plus spécifiques telle que l'érysipelothrix rhusiopathiae associée aux poissons, à la volaille, au lapin et aux porcs, mais il ne semble pas que ces agents bactériens spécifiques soient si fréquents. Cette infection ressemble à l'érysipèle et apparaît souvent suite à des traumatismes mineurs.

8.3.4 Prévention des infections

La prévention des infections et autres maladies de la peau dans l'alimentation demande une surveillance régulière. L'idéal serait d'avoir une infirmière sur place, mais comme les entreprises sont trop petites, nous devons souvent avoir recours au secouriste. Il semble présentement que bien des individus maintiennent des lésions cutanées qui n'existeraient pas avec un bon contrôle médical. En l'absence d'un suivi régulier jusqu'à la guérison, la prévention sera difficile. La coopération de l'employeur et des travailleurs est obligatoire, car si l'un ou l'autre tolère les infections et les dermatoses au travail, tous les efforts sont inutiles.

Dermatoses

Bibliographie

- * ADAMS, R.M., "Dermatitis in Food Service Workers", *Allergy Proceedings*, vol. 11, no. 3, (mai-juin 1990).
- * FLEMING, D., "Dermatitis in Grocery Workers Associated with High Natural Concentrations of Furanocoumarins in Celery", *Allergy Proceedings*, vol. 11, no. 3, (mai-juin 1990).
- HANSEN, K.S., "Protein Contact Dermatitis in Slaughterhouse Workers", *Yearbook of Occupational Environmental Medicine*, p. 104, (1991).
- * HAYASHI, M., "Dermatoses Among Poultry Slaughterhouse Workers", *Am. J. Ind. Med.*, vol. 15, pp. 601-605, (1989).
- HANNUKSELA, M., "Immediate reactions to fruits and vegetables", *Contact Dermatitis*, vol. 3, pp. 79-84, (1977).
- MAIBACH, H.I., *Occupational and Industrial Dermatology*, Year Book Medical Publishers, (1987).
- * NETHERCOTT, J.R., HOLNESS, D.L., "Occupational Allergic Contact Dermatitis", *Clinical Reviews in Allergy*, vol. 7, pp. 399-415, (1989).

* Articles joints

Permatitis in Food Service Workers

Robert M. Adams, M.D.

Food service workers are more likely to have irritant than allergic skin reactions. Immediate hypersensitivity exists to fruits, vegetables, seafood, and raw meats, and occasional anaphylactoid reactions occur to apples, potatoes, mustard, and sulfites. Delayed hypersensitivity is less common and usually is caused by garlic, onion, and various spices and preservatives.

In California in 1983, the total number of agricultural reports of worker-related diseases was 3,732; 2,080 or 55.7% of these were skin conditions. Of these 87% occurred in agricultural production, pest control, and other crop and soil services. One-third of the total were caused by poison oak; one-third by chemicals; and one-third by soaps, detergents, plants, infections, and so forth.

Enormous amounts of pesticides are used every year in the farming industry in California. It is important to realize that the concentration of the active ingredient in a pesticide may be as low as 1%, or as high as 40% and that its carrier (toluene, xylene, kerosene, etc.) may play an equally important role in provoking a skin condition. A pesticide with carrier placed undiluted on the skin, covered for 48 hours, will almost always result in an irritant reaction because of the presence of the irritating fuel oil, surfactants, and even "inert" materials. Therefore, in testing for pesticide sensitivity, it is important to use only the active ingredient, which is difficult to obtain, and the correct test concentrations are often unknown. Many skin conditions may be caused by pesticides: irritant and allergic contact dermatitis, photodermatitis, folliculitis, ulcerations, pigmentary changes, erythema multiforme, urticaria, and porphyria. As an example of irritation, a farmer accidentally sprayed with a pesticide and carrier developed a severe blistering reaction because he was unable to

change his clothing immediately. He developed a permanent scar that was still present 10 years after the accident.

The use of a short hoe contributes to close contact with plants and pesticides and also may be an important factor in any resulting skin irritation.

Between 1977 and 1981, the pesticides most commonly reported in California as having caused dermatitis were elemental sulphur, Omite, Betamil, Roundup, weedoil, and methyl bromide. About 90 orange-pickers in the southern part of California's Central Valley developed dermatitis from contact with Omite. Other contact allergens used in the pesticide industry are Maneb and Zineb, which are related to rubber accelerators. Patients who are sensitive to rubber gloves can therefore be sensitive to these two allergens and to other pesticides, such as Thiram. In addition, sunlight exposure, particularly in older workers taking antihypertensive medications, can induce eczematous eruptions.

In bakers, the wet, sticky dough is a common cause of irritation often ignored by the handler. Contact allergy is rare among bakers, but it has been reported from malt flour, rye, and wheat. Food dyes rarely cause allergic reactions, but flavors, especially cinnamon, may cause sensitization. Sodium metabisulfite is also a contact allergen and should be tested only at 1% concentration. The most common dermatitis (next to simple irritant dermatitis caused by soaps and detergents) among bakers is *Candida* in the finger webs. *Candida* is a common cause of infection among bakers and food service workers. Food mites in flour or sugar occasionally cause epidemics of a pruritic dermatitis. Irritant dermatitis from disinfectants and glass cleaners is common in wet work such as bartending. Juices of limes and lemons are also irritants and may evoke photosensitive reactions. Butchers and poultry workers also experience *Candida* infections, dermatitis from rubber in gloves and aprons as well as from penicillin residues, and irritation from cleaning agents. Friction calluses as well as injuries from broken chicken bones are com-

Clinical Professor, Department of Dermatology, Stanford University

mon. Erysipeloid has been reported, virus warts are common, and contact urticaria may occur from raw meats, particularly liver. Moniliasis is common among cannery workers because of the wet work; allergic sensitization may occur from rubber gloves and boots. Irritant dermatitis from fruits and vegetables is common, and contact urticaria from their cut surfaces occurs occasionally. Sodium metabisulfite may induce contact dermatitis in canneries where it is used as an antioxidant (to keep cauliflower white, for example). Dairy workers may experience dermatitis from antibiotics as well as bacterial and viral diseases. Food preparation workers often acquire contact urticaria, which is often misdiagnosed, from meats, seafoods, fruits, and vegetables. Raw apples have been reported as causing anaphylactoid reactions in patients with contact urticaria, and swelling of the lips and tongue in some who have eaten them. Raw potato is a common cause of contact urticaria, and mustard causes both Type I and delayed hypersensitivity reactions. The gallate preservatives and sodium metabisulfite used to keep potatoes white may also cause problems.

E. Cronin of England states that, among food workers, the most common cause of Type I reaction is fish, while the most common cause of Type IV reaction is garlic. N. Hjorth agrees and also includes onion and various metals as causes of the Type IV reaction. Garlic shows a typical reaction on the first three fingers and thumb of the hand that holds the garlic.

Testing for contact allergy to foods should be done using only the freshest materials and not those prepared by commercial companies.

Type I reactions have been neglected by dermatologists, but lately there has been increased interest in their importance.

DISCUSSION

In response to a question from the audience, Adams said that there are several protective creams for

poison ivy on the market. He expressed skepticism concerning these creams, because the greatest problem with poison oak and ivy is not so much from contact with the skin but from later reactions resulting from the resin contamination of clothing. The reactions seen are often perpetuated by the presence of the contaminant, particularly on shoes. Application of a cream, therefore, will not prevent a later reaction to the residue on clothing after the cream has worn off. It may be of some benefit to workers who have isolated periods of contact and are careful in removing their clothing and shoes, but it will probably not be effective for the general population. A member of the audience asked if there are differences in sensitivity among various areas of the skin chosen for the patch test. Adams responded that the back is the most sensitive area, and the next most sensitive is the outer aspect of the arm. The reactivity varies considerably as the patch test is moved from the arm to other areas of the body. For example, a test with 10% glutaraldehyde on the sole will give no reaction, whereas 1% on the back will give a good allergic reaction. The forearm is less sensitive but is used occasionally.

A member of the audience said that many of the vehicles employed in the patch test could potentially denature protein antigens. Adams said that he had not observed this phenomenon because the allergens used are low-molecular-weight compounds.

REFERENCES

1. Adams RM. Occupational Skin Disease. 2nd ed. Philadelphia: W. B. Saunders, 1989.
2. Cronin E. Dermatitis of the hands in caterers. *Contact Dermatitis* 17:265-269, 1987.
3. Hjorth N. Battery for testing of chefs and other kitchen workers. *Contact Dermatitis* 1:63, 1975.
4. Peltonen L, Wickström G, Vaahtoranta M. Occupational dermatoses in the food industry. *Dermatosen* 33:166-169, 1985. □

Dermatitis in Grocery Workers Associated with High Natural Concentrations of Furanocoumarins in Celery

David Fleming, M.D.

Fleming suggested that epidemiology is the best analytic tool for studying something one knows little about. His presentation had three purposes: 1) to give a feel for the practicalities of an epidemiologic investigation and what epidemiology can offer various disciplines; 2) to discuss the specific problem of phytophototoxic dermatitis in produce workers; and 3) to illustrate the type of problems encountered more often as the science of food technology becomes increasingly sophisticated.

Fleming described an unusual case of occupational dermatitis among grocery workers. A large number of employees of a major chain of supermarkets (chain X) developed a relatively severe skin rash. A team consisting of the Special Pathogens Branch of the Centers for Disease Control (CDC), the National Institute for Occupational Safety and Health (NIOSH), and the State in which the outbreak occurred was assembled. It found that 30 of 127 workers had a vesicular peeling rash on the hands, arms, and interdigital areas that occurred in linear streaks perpendicular to the axis of the forearm. As the lesions healed, hyperpigmentation developed. A dermatologist felt that the rash was typical of a phytophototoxic dermatitis caused by contact with plants that contain light-sensitizing compounds and subse-

quent exposure to activating wavelengths of the ultraviolet spectrum.

The case definition classified a worker as suffering from this condition if there were 1) dark spots or streaks on the hands or arms, 2) pimples containing fluids on hands or arms, or (3) blisters on arms and one or more of red skin, itchy skin, or dry or cracked skin. Anyone meeting these criteria who exhibited the symptoms before working at the store was excluded from the study. Three methods were used to identify additional cases in the geographic area investigated: 1) all registered practicing dermatologists were surveyed and asked to report such cases; 2) a letter was sent to all practicing physicians requesting reporting; and 3) media attention alerted the public to the study.

The team focused its attention on two stores reporting the greatest incidence of problems. As a result of administering questionnaires to the employees, 30 cases (24%) out of a total of 126 respondents were identified.

The problem began in the winter and spring, peaked in the summer, and tapered off by the time the study began—a problem often encountered in epidemiologic investigations. One-fourth of the subjects with the condition reported multiple episodes of the rash problem. There was a significantly increased attack rate in young workers, but no other differences could be identified with respect to sun exposure, tanning characteristics, and types of clothing, sex, or hand-washing practices between those affected and those who were not. There was one major difference. The degree of illness was

Deputy State Epidemiologist, Oregon State Health Division

strongly influenced by job type. In particular, the highest incidence occurred among the produce workers at one store (100%), with clerks, baggers, and checkers next, and with specialty workers least affected. Therefore, the focus moved to the produce workers and to the types of special produce they were handling.

There was a problem in trying to separate exposure to the possibly toxic vegetables from exposure to the benign. Celery had the highest potential risk, although some other vegetables also were suspected. Using several different analytic techniques, there was a significant association of disease with celery after controlling for contact with other vegetables such as spinach, parsley, and parsnips. The workers who had contact with celery had the highest dose-response effect. The evidence pointed, therefore, to exposure to celery as at least one of the culprits in this illness because 1) the highest relative risk of disease was associated with celery, 2) the strongest linear trend in dose-response effect in workers was in contact with unbagged celery, and 3) when stratified by exposure to certain vegetables, celery was the most implicated. In addition, there was anecdotal evidence. One worker skin tested himself overnight with a small piece of celery. The next day, he exposed the tested area to the sun, and a typical blistering lesion appeared. Another worker with a severe case stopped working with celery but continued contact with other produce. His problem resolved over the course of a week.

The association of celery with dermatitis was also biologically possible. Celery dermatitis was associated with celery harvesting as long ago as 1924. Twenty years later, an English investigator suggested that this dermatitis in harvesters might also be dependent on exposure to ultraviolet radiation. In 1961, furanocoumarins were identified as the causative agent. Furanocoumarins are a subgroup of substances known as psoralens, naturally occurring compounds found in celery, parsnips, and citrus fruits. Exposure to any of these plants followed by exposure to ultraviolet radiation can cause photodermatitis. Furanocoumarins are used by the medical profession in this country to treat certain skin disorders such as psoriasis, and they are also known carcinogens. They have been used since the days of ancient Egypt to treat skin disorders such as vitiligo. These compounds are thought to act as phytoalexins, chemicals produced by a plant in response to disease or injury—the corticosteroids of the plant world.

Outbreaks of celery dermatitis in the past were confined to field workers and linked with high concentrations of furanocoumarins produced by celery infected in the fields with a mold of the genus *Sclerotinia*, known as "pink rot" in the celery industry. However, Fleming explained that the outbreak studied in this case was not

occurring among celery harvesters and was resulting from exposure to apparently healthy celery. Several additional bits of evidence implicated a certain brand of celery (brand A). The management of the grocery chain had no problem until it started carrying brand A celery, a variety known for its disease resistance and high quality. At one other independent grocery that claimed not to have carried brand A, it was found that they had inadvertently received one pallet of brand A celery coincidental with an outbreak of dermatitis in the produce workers. The problem disappeared when the store returned to carrying its original brand.

As word got out about the study, several similar outbreaks of dermatitis were discovered. In 1980-81, NIOSH had investigated an outbreak of dermatitis in grocery workers in Ohio. The cause was not identified at that time, but it was found during the current study that the Ohio store had carried brand A celery. In 1984, another outbreak in Minnesota occurred. Again, the Minnesota store had carried brand A.

The association of brand A celery and dermatitis was assessed by a survey of chain X stores. Produce managers and workers were surveyed via questionnaire in 77 stores in 17 States. Ninety-six percent of the stores responded. In 13 of 17 states, there existed a 26% attack rate among workers. The states were predominantly in the West. There was a significant association between stores that carried brand A celery and illness in workers.

What is special about brand A celery that causes it to be associated with dermatitis in produce workers? Phytophototoxic dermatitis is caused by exposure to furanocoumarins produced in response to stress to a plant. Brand A was specially bred for disease resistance and high quality. In a blind analysis of three brands of celery including brand A, brand A contained significantly higher native levels of furanocoumarins than the others.

In summary, Fleming noted that, in this outbreak of phytophototoxic dermatitis, produce workers were at highest risk, and exposure to celery was significantly associated with illness. In contrast with previous reports, produce workers, as opposed to field harvesters exposed to diseased celery, were the most affected. The nationwide survey indicated that the problem was common in many areas, and a particular brand of specially bred celery could be implicated. This brand had significantly higher levels of furanocoumarins than other brands. In breeding, selection of a disease-resistant strain may have inadvertently resulted in plants with increased levels of furanocoumarins. It is not known, however, what effect harvesting, storing, transporting, and use of pesticides might have had on the level of furanocoumarins.

Other outbreaks have occurred as a result of exposure to brand A. In a recent Oregon case, tanning salons

were identified as a cofactor. Those most affected were workers who handled celery and immediately patronized a tanning salon.

Further studies are required to determine factors associated with furanocoumarin production in celery, to evaluate the possible effects of consumption of high levels of furanocoumarins by man, and to define methods to prevent phytophototoxic dermatitis in celery workers.

DISCUSSION

In response to a comment from the audience about breeding vegetables that contain large amounts of carcinogenic compounds, Fleming said that the known carcinogenic potential of psoralens is limited to exposure on the skin followed by exposure to ultraviolet light. It is hard to extrapolate this effect to that which might result from ingestion. The likelihood of exposure of the GI tract to ultraviolet light is low. The issue needs to be examined, but the Federal regulatory agencies have decided that ingestion of furanocoumarins is not theoretically sufficiently dangerous to warrant limiting the amount of celery ingested.

A member of the audience asked why the problem did not show up in the celery harvesters. Fleming noted that brand A is a common brand and that its producers would not allow the investigating team to question the harvesters about possible problems. Therefore, it was not possible to determine whether or not they were experiencing rash. Because the problem has been known to exist in the harvesting business, theoretically the workers are taking precautions such as wearing gloves and long sleeves. It is also known that furanocoumarins continue to be produced in cut celery, so that storage practices may result in higher levels of the compounds in the celery when it reaches the store than when it is harvested.

Adams said that the checkers move the celery over a light of 550 or 600 Å, including a certain amount of ultraviolet in the 400-Å range, and asked if dermatological reactions in checkers were related to this light. Fleming felt that the excess of cases of dermatitis in checkers was more likely due to their high exposure rate to the celery than to use of checkout lights.

A member of the audience commented that, in 1961, Birmingham reported phototoxic bullae among celery harvesters, and the report of this outbreak in the *Annals of Internal Medicine* occurred 25 years later. He questioned why there were no reports in the interval. Fleming thought that the dermatitis was sufficiently common in harvesters that no one was commenting on it until the higher levels in the new breed of celery began to affect produce workers.

Another member of the audience asked if hypersen-

sitivity reactions were found among people ingesting this celery. Dr. Fleming said no such reactions were found.

In response to the question of why people in the meat department reported dermatitis, Fleming indicated that there was some crossover between departments, depending on a given department's need to borrow workers from other areas. Therefore, the meat workers spent a small but significant amount of time in the produce department.

Marzulli asked Adams if the new patch test kits have nickel in water or in petrolatum and in what concentration. Adams responded that the TRUE-test uses an inert, common cosmetic polyethylene vehicle of some type, but that testing of it before marketing showed an even distribution of the nickel throughout the test material. The FDA is near approval and having problems, but not with the nickel. The nickel concentration is 2.5%.

Cohen asked if contact urticaria is strictly a local phenomenon or a localized manifestation of a systemic sensitivity. He added that the list of substances causing urticaria is not necessarily the same as the list of substances most prevalent in systemic hypersensitivity. He also asked if one would expect urticaria to be revealed by a prick test or by only a patch test. Adams and Marzulli agreed that topical application (not a scratch) and occasionally prick testing are used. Zeitz added that he had had an opportunity to test people with nickel sensitivity (local contact urticaria to nickel) and that a usual patch test elicits contact urticaria in 15 to 30 minutes. He stated that he would be reluctant to use a prick test with nickel in patients who have nickel-induced contact urticaria.

REFERENCES

1. Berkley SF, Hightower AW, Beier RC, et al. Dermatitis in grocery workers associated with high natural concentrations of furanocoumarins in celery. *Ann Intern Med* 105:351-355, 1986.
2. Pathak MA, Daniels F, Fitzpatrick TB. The presently known distribution of furanocoumarins (psoralens) in plants. *J Invest Dermatol* 39:225-239, 1961.
3. Beier RC, Ivie GW, Oertli EH. Psoralens as phytoalexins in food plants of the family Umbelliferae. *Food Plants* 19:296-309, 1983.
4. Birmingham DJ, Key MK, Tubich GE. Phototoxic bullae among celery harvesters. *Arch Dermatol* 83:128-141, 1961.
5. Austad J, Kavil G. Phototoxic dermatitis caused by celery infected by *Sclerotinia sclerotiorum*. *Contact Dermatitis* 9:448-451, 1983.
6. Centers for Disease Control. Outbreak of phototoxic dermatitis from limes—Maryland. *MMWR* 34:462-464, 1985.
7. Centers for Disease Control. Phototoxic dermatitis among grocery workers—Ohio. *MMWR* 34:11-13, 1984.
8. Stern RS, Laird N, Melski J, Parrish JA, Fitzpatrick TB, Bleich HL. Cutaneous squamous-cell carcinoma in patients treated with PUVA. *N Engl J Med* 310:1156-1161, 1984. □

Dermatoses Among Poultry Slaughterhouse Workers

Masato Hayashi, MB, Megumi Saitoh, MB, Nobuo Fujii, MD,
Yasuo Suzuki, MD, Keitaro Nishiyama, MD, Seiichiro Asano, MB, and
Hisashi Hayashi, MD

A survey on the incidence of occupational dermatoses among poultry slaughterhouse workers, who, in order to do their work more efficiently, protected their hands only with cotton gloves, revealed that many workers had dermatoses of the hands.

Their symptoms included maceration, erosio interdigitalis, paronychia, trichophytia unguium, and eczema, presumably caused by the constant wetness of their hands during work. *Candida albicans* was detected in the ungual lesions of some patients.

A second survey including a skin examination was performed at a plant where preventive measures such as better working gloves and improved sanitary conditions had been implemented because of the high incidence of skin disorders. The results of this survey showed marked improvement in the reduction of the incidence of dermatoses.

Key words: occupational dermatoses, preventive measures, incidence reduction

INTRODUCTION

Poultry processing workers usually do their work wearing thick rubber gloves, or sometimes wire-mesh gloves, to protect their hands from mechanical injuries caused by sharp tools or bones and from dermatoses due to wet working conditions. However, there have been reports of various disorders occurring among them in spite of protective measures [Cohen, 1974; Boren and Leky, 1979; Mergler et al., 1982; Marks et al., 1983].

The disadvantage of these types of protective gloves is that they blunt the tactile sense of the fingers. Since work in the poultry industry is mostly carried out on assembly lines, where skillful manual work is required, workers frequently choose not to wear gloves that hinder movement and sense of touch. There have also been many reported cases of wounds when wearing gloves [Cohen, 1974; Marks et al., 1983] as well as allergic dermatitis caused by the constant wearing of rubber gloves [Marks et al., 1983]. Since no appropriate prophylactic method has been found, it is difficult to completely prevent hand dermatoses in poultry workers.

Department of Hygiene, School of Medicine, The University of Tokushima, Tokushima 770, Japan (M.H., M.S., N.F., Y.S., K.N.).

Department of Dermatology, School of Medicine, The University of Tokushima, Tokushima 770, Japan (S.A., H.H.).

Address reprint requests to K. Nishiyama, Department of Hygiene, School of Medicine, The University of Tokushima, Tokushima 770, Japan.

Accepted for publication December 8, 1988.

In the present study, an initial survey was performed to determine the actuality of dermatoses occurring in workers who, to improve their work efficiency, wore only cotton gloves. Then, a second survey was conducted to investigate the effect of preventive measures such as improved gloves and better environmental conditions in a plant that had adopted these measures. The results of the second survey revealed a marked improvement in the occurrence of dermatoses.

METHODS

The first survey was performed at four slaughterhouses (plants A–D) in Tokushima prefecture. Each plant had 100–200 workers and processed 10,000–20,000 chickens every day by an assembly-line system. After the chickens, suspended from a chain, had been put through the processes of killing, bloodletting, plucking, and evisceration, the meat and viscera were treated and processed, then sent to packing and shipping sections. Most workers wore cotton gloves, which provided them with a better grip. They washed their hands with medicated soap during periodic work recesses.

The first survey, which included a medical examination, was undertaken on 527 workers in plants A–D from May to August 1983. More than 90% of the employees in each plant were examined. The examination consisted of an interview and a skin inspection. Pathogen specimens were collected from ungual lesions of some of the patients.

Since the results of the medical examination indicated an extremely high incidence of dermatoses, we offered guidance in preventive measures in cooperation with the supervisory authorities. In response to our suggestions, in June 1986, plant A instructed workers via a prevention manual to wear disposable polyethylene gloves under their usual cotton gloves and between 1986 and 1987, remodeled its dining room, lounge, washing recesses, and lavatories, making them lighter and cleaner. In January 1988, a second survey was performed at plant A to examine the effects of these measures.

RESULTS

The results of the first survey (1983) are shown in Tables I–IV. In these tables, the results obtained in plant A are shown so as to be comparable with those obtained in the other plants. No distinctly different results were observed among the other plants.

Table I shows the incidence of dermatoses according to occupational category. Among 527 examinees, 343 (65.1%) presented with skin symptoms. In particular, 70–80% of women who were engaged in the treatment and processing of meat, treatment of viscera, or packing had symptoms. Table II shows the incidence of dermatoses according to symptoms. Maceration and *erosio interdigitalis* were the highest in frequency, followed by paronychia and pompholyx. Eczema was relatively uncommon. *Candida albicans* was detected from the ungual lesions in six out of ten workers in plant A.

The interval between employment and the manifestation of skin symptoms was less than 3 months in about 50% of the workers (Table III). Responses to questions concerning preventive and/or therapeutic measures for dermatoses are presented in

TABLE I. Prevalence of Poultry Slaughterhouse Workers With Skin Symptoms According to the Type of Work

Type of work	Plant A				Plants B-D			
	Male		Female		Male		Female	
	n/n ^a	(%)	n/n	(%)	n/n	(%)	n/n	(%)
Office, supervision	1/8	(12.5)	1/7	(14.5)	0/13	(0)	0/11	(0)
Pretreatment ^b	11/14	(78.6)	38/51	(74.5)	42/69	(60.9)	192/252	(76.2)
Treatment of viscera and meat ^c	0/0	(—)	10/12	(83.3)	0/1	(0)	17/22	(77.3)
Packing	0/2	(0)	6/8	(75.0)	3/10	(30.0)	10/12	(83.3)
Others	0/0	(—)	3/7	(42.9)	5/19	(26.3)	4/9	(44.4)
Total	12/24	(50.0)	58/85	(68.2)	50/112	(44.0)	223/306	(72.9)

^aNumber of workers with symptoms/number of workers examined.

^bIncludes killers, pickers, openers, pullers, eviscerators, and meat cutters.

^cThe final steps in the process before packing.

TABLE II. Prevalence of Specific Dermatoses Among Poultry Slaughterhouse Workers

Symptom	Plant A		Plants B-D	
	Male	Female	Male	Female
Affected subjects	12	58	50	223
Maceration	5 (41.7)	26 (44.8)	26 (52.0)	112 (50.2)
Erosio interdigitalis	3 (25.0)	16 (27.6)	17 (34.0)	99 (44.4)
Paronychia	0 (0)	14 (24.1)	7 (14.0)	44 (19.7)
Pompholyx	2 (16.7)	2 (3.4)	11 (22.0)	13 (5.8)
Trichophytia unguium	1 (8.3)	10 (17.2)	3 (6.0)	11 (4.9)
Eczema	1 (8.3)	4 (6.9)	2 (4.0)	9 (4.0)
Others	0 (0)	3 (5.2)	3 (6.0)	9 (4.0)
Total no. dermatoses	12	75	69	297

Nos. in parentheses indicate percentages of affected subjects.

Table IV. About 50% of affected workers received treatment by physicians, whereas approximately 40% were untreated. Many of the workers hand-washed and applied hand cream to prevent symptoms. Only about 14% used cotton gloves as a preventative measure.

In the first survey, as shown in Tables I-IV, no distinct differences were apparent between plant A and the other plants in the incidence of each item surveyed.

The results of the second survey (1988), which was performed at plant A after implementation of preventive measures, are shown in Table V together with the results of the first survey, which was conducted before the measures were taken. The incidence of workers with symptoms, which had been 64.2% before the measures were undertaken, had decreased significantly ($p < .01$) to 26.0%. This decrease was not due to a survivor effect, because the numbers of workers who had retired during the period after the first survey were 21 (30%) of 70 affected subjects and 18 (46.2%) of 39 nonaffected subjects. Changes in symptoms were studied in 70 workers examined in both surveys, and disappearance of symptoms was noted in 32 (65.3%) of 49 workers who had symptoms at the time of the first survey. The rate of disappearance was 76% for maceration, 73% for erosio interdigitalis, 23% for paronychia, and 50% for trichophytia unguium. In contrast, only two workers developed new symptoms: maceration in one and dyshidrosis in another. These

TABLE III. Interval Between Employment and Manifestation of Symptoms in Poultry Slaughterhouse Workers

Interval	Plant A		Plants B-D	
	No.	%	No.	%
Before	8	11.8	2	0.8
0-3 mo	41	60.3	130	51.2
4 mo-1 yr	3	4.4	28	11.0
1-2 yr	6	8.8	23	9.1
2-3 yr	4	5.9	19	7.5
3-5 yr	2	2.9	18	7.1
5-7 yr	1	1.5	15	5.9
7-9 yr	1	1.5	11	4.3
9 +	2	2.9	8	3.1
Total	68	100.0	254	100.0

TABLE IV. Rates of Subjects Undertaking Treatment and Preventive Measures for Dermatoses

	Plant A		Plants B-D	
	No.	(%)	No.	(%)
Treatment				
Total subjects*	69	(100)	259	(100)
Medication by physician	26	(37.7)	135	(52.1)
Self-medication by drug	9	(13.0)	29	(11.2)
Untreated	34	(49.3)	95	(36.7)
Preventive measures				
Total subjects*	39	(100)	209	(100)
Cotton gloves	6	(15.4)	28	(13.4)
Hand cream	19	(48.7)	66	(31.6)
Hand-washing	19	(48.7)	116	(55.5)
Drug	6	(15.4)	52	(24.9)

*No. subjects who had dermatosis and who responded to questionnaire.

TABLE V. Prevalence of Dermatoses Among Subjects in Plant A Examined in 1983 and/or 1988

	Total	Positive findings in 1988*	Negative findings in 1988*
Total subjects examined in 1983	109 (64.2%, or 70, positive)	—	—
Subjects examined in 1983 only	39 (53.8%, or 21, positive)	—	—
Subjects examined 1983 and 1988	70	19 (27%)	51 (73%)
Positive findings 1983	49	17 (35%)	32 (65%)
Negative findings 1983	21	2 (10%)	19 (90%)
Total subjects examined 1988	123	32 (26%)	91 (74%)
Subjects examined 1988 only	53	13 (25%)	40 (75%)

*Nos. parentheses indicate percentage of row total.

changes in the incidence of symptoms were statistically significant ($p < .01$) and indicated the effectiveness of the preventive measures.

DISCUSSION

The incidence of dermatosis of the hand was very high (70-80%) among workers who wore only cotton gloves while handling poultry meat. Analysis of

symptoms showed that maceration was most prevalent, occurring in about 50% of workers, followed by erosio interdigitalis (40%) and paronychia (20%). These are nonspecific disorders associated with "wet work" and are caused mainly by constant wetness of the hands. Since *Candida albicans* was detected from the ungual lesions of some patients, erosio interdigitalis and paronychia may have been caused by fungi. Marks et al. [1983] also noted a higher frequency of *Candida* infections than in other types of disorders and symptoms. Hand-washing with medicated soap after work seemed to have little effect. The higher proportion of female workers with symptoms may have been due to the longer exposure to wet conditions in comparison with male workers because of the type of work done and their involvement in cooking and washing at home. Harrington [1981] reported contact dermatitis associated with chicken meat and skin, and contact urticarial reactions to chicken muscle and heart were reported by Beck and Nissen [1981]. However, Marks et al. [1983] found no workers with such hypersensitivity in their study. Since eczema was less common and complaints of other allergic symptoms were rarely reported during the medical examination in the present study, there seemed to be no allergens specific to the work process.

Virus warts have been reported to occur frequently in meat handlers, including poultry workers [Wall et al., 1981; Mergler et al., 1982]. Mergler et al. [1982] concluded that abrasion of the skin (too large gloves) and high humidity facilitate cutaneous infection by such viruses. In the present study, no warts were found among the examinees.

Since it was obvious that constant wetness of the hands caused symptomatic manifestations, workers in plant A began to wear polyethylene gloves, which were changed frequently (five to six times per day), under their usual cotton gloves. In addition, a clean, well-lighted environment was provided by remodeling lounges, dining rooms, washing recesses, and lavatories. This may have encouraged workers about maintaining cleanliness. The overall effects of these measures were obvious in the results of the second medical examination of workers in plant A. Nevertheless, a few workers showed no improvement of maceration, and there were some who developed new symptoms. It is likely that some of them had difficulty in keeping their skin dry because of the nature of their work, while others did not follow the instructions in the prevention manual. For such cases, appropriate steps, including the use of effective gloves and/or changes in work processes for the former and strict supervision for the latter, should be taken in the future, especially since the cure rates of paronychia and trichophytia unguium are rather low and radical treatment is necessary for managing these disorders.

REFERENCES

- Beck HI, Nissen BK (1981): Type I and type IV allergy to specific chicken organs. *Contact Dermatitis* 8:217-218.
- Boren SD, Leky BJ (1979): Dermatitis in duck workers. *J Fam Pract* 9:951-952.
- Cohen SR (1974): Dermatologic hazards in the poultry industry. *J Occup Med* 16:94-97.
- Harrington CI (1981): Chicken sensitivity. *Contact Dermatitis* 7:126.
- Marks JG, Raicny CM, Raicny MA, Andreozzi RJ (1983): Dermatoses among poultry workers: "Chicken poison disease." *J Am Acad Dermatol* 9:852-857.
- Mergler D, Vézina N, Beauvais A (1982): Warts among workers in poultry slaughterhouses. *Scand J Work Environ Health* 8:180-184.
- Wall LM, Oakes D, Rycroft JG (1981): Virus warts in meat handlers. *Contact Dermatitis* 7:258-267.

Occupational Allergic Contact Dermatitis

James R. Nethercott^{*1} and D. Linn Holness²

¹*Division of Occupational Health, School of Hygiene and Public Health, The John Hopkins University, Baltimore, MD; and*

²*Department of Occupational and Environmental Health, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada*

One can deem a dermatitis to be occupational contact dermatitis when work exposure can be shown to be a major causal or contributory factor in the genesis of the pathological process in the skin (1). Contact dermatitis constitutes a proportion of compensable disease in most jurisdictions where data have been collected (2). Odland has stated that the proportion of paid compensation claims for occupational skin disease in various American states varied between 40 and 60% (3). Between 1972 and 1976, 40% of industrial disease reported in the US was dermatological (4). Keil and Shmunes reported that 83% of industrial disease claims in South Carolina were dermatological (5). Skin disease constituted 65% of industrial disease claims in the UK in 1977, with the majority of these being occupational contact dermatitis (6).

The above figures are based on paid claims. There may be reason to believe that they may significantly underestimate the prevalence of such disease in the workplace. The disparity between the apparent prevalence of dermatitis and that deemed to be work-related and warranting compensation likely relates to a number of factors. For instance, severity is important. It determines what may be accepted as an acceptable "biological effect" of the environmental factors in a job vs what constitutes "a disease." Chapping of the hands in those doing wet work could be taken to represent the former and may not be perceived as disease by the worker or others. The criteria used to award compensation are other factors that vary from jurisdiction to jurisdiction and may affect these figures.

^{*}Author to whom all correspondence and reprint requests should be addressed.

In 1987, Meding and Swanbeck reported that 11% of 16,584 respondents surveyed in an industrial city in Sweden reported having hand dermatitis or having been troubled by it in the preceeding year (7). Based on a national health survey of 14,667 respondents, Kavli and Ford reported a prevalence of allergic contact dermatitis of 8.9% in Norwegians (8). In the same study, they found that 14% of women who listed housework as their primary occupation reported having contact dermatitis. A prevalence of hand dermatitis, varying between 6 and 7%, was reported in populations surveyed in the Netherlands by two other groups of investigators (9,10).

The prevalence of contact dermatitis in different occupational groups has been reported by a number of investigators. In Swedish construction workers, Wahlberg reported that 18% either had work-related contact dermatitis or gave a history of it (11). In a 1980 study of Swedish house painters, Hogberg and Wahlberg found a 3.9% prevalence of contact dermatitis (12). Varigos and Dunt reported a prevalence rate of 6.8% in cement workers and 3.7% in rubber workers in Australia (13). A survey carried out by the US National Hairdressers and Cosmetologists Association revealed that half of 450 respondents reported contact dermatitis associated with the handling of shampoos, permanent waving solutions, and colorants (14). Estlander et al. reported that in a postal survey of 106 dental technicians, of which 88% responded, 30% reported having had contact dermatitis during their career, whereas 19% were currently affected (15). In a study of Finnish hospital workers, Lammintausta et al. found that 1% of 2290 hospital workers assessed reported experiencing contact dermatitis associated with their work, whereas 46% of 536 workers performing jobs involving wet work reported contact dermatitis (16,17). In a study of 250 Indian tie and dye factory workers, Mathur et al. reported that 19.6% were found to have incapacitating contact dermatitis of their hands (18).

Although it is estimated that approximately 80% of occupational contact dermatitis is irritant in origin in terms of numbers, allergic contact dermatitis remains a significant work-related disorder (19,20). Jordan reported that 26% of his hand dermatitis cases were allergic (21). In Singapore, Goh and Soh reported that 32.6% of 377 occupational contact dermatitis cases they assessed were allergic (22). The prevalence of allergic contact dermatitis reported

as a proportion of those with contact dermatitis varies. Wilkinson et al. reported that 51% of the patients they investigated with contact dermatitis of their hands were allergic in origin (23). In 457 consecutive cases of occupational contact dermatitis evaluated by the authors in Toronto, Canada, 49.5% were deemed to be allergic. Occupational contact dermatitis is common, and an allergic basis for the process can often be found.

CLINICAL FEATURES

The clinical features are distinctive, but not pathognomonic (24–27). Acute allergic contact dermatitis is characterized by erythema, edema, scaling, and vesicle formation in the skin at the site of contact with the offending allergen. The eruption begins 1–2 d after exposure. If there is no further contact, the eruption resolves in 1–2 wk and may leave postinflammatory hyperpigmentation. Without further exposure, the process is short lived. If one can identify the cause and avoid it, the problem should not be an ongoing one.

The more common occupational problem, certainly the one causing the greater difficulty for affected workers and their physicians, is chronic dermatitis that develops following prolonged exposure to a contact allergen. In this instance, the clinical picture is one of a lichenified erythematous scaling eruption in confluent patches with indistinct borders. The majority of patients present with the eruption on the hands. It may be palmar or dorsal, though the latter is more characteristic. These patients often have a protracted course even if they conscientiously endeavor to avoid further contact with the allergen(s) implicated in their disease. The question of whether the allergic contact allergy is the primary event or an epiphenomenon superimposed on a constitutional eczematous process is often questioned.

Thus, there are two distinct clinical presentations of occupational allergic contact dermatitis. They have contrasting natural histories and present different problems in terms of management.

INVESTIGATIONS

The *sine qua non* in the diagnosis of occupational allergic contact dermatitis is the patch test (28). The International Contact Derma-

titis Research Group (ICDRG) has recommended a standard method for this test and its interpretation (29). Standardized concentrations for such tests have been published for many environmental substances (30-33). These concentrations have been established largely by tests carried out on patients affected with dermatitis or small numbers of control subjects. Even when the test is performed with the recommended methodology and at generally accepted concentrations, false positive or false negative tests still occur.

Evaluation of the test site requires considerable discretion since one must differentiate between an acute irritant contact response that has a sharp border and resolves after the patch is removed and a faint allergic response characterized by persistent macular erythema when the patch is first removed and becomes more pronounced with observation. It is essential that the patch test sites be reexamined at least once after the patch is removed at 48 h. Whether one carries out the second reading at 96 h or as late as seven days is not presently considered to be crucial. False positive and false negative responses are not uncommon when testing with conventional test substances and pose a greater problem when testing with industrial chemicals for which established patch test concentrations may be unavailable or less reliable (34-36). Other problems that may pose a problem in interpretation include the excited skin syndrome (37,38) and multiple concomitant positive responses (39).

Patch testing with industrial chemicals presents a special challenge. Unlike other circumstances, the results often are of medicolegal significance in terms of compensation and, if positive, the tests may be important to the patient's livelihood in terms of continuing their occupation. Furthermore, the individual chemicals, blends of chemicals, or combinations of exposures in the workplace pose problems for the clinician in terms of how to carry out the tests and how to interpret them. Manufacturers are required by the Occupational Health and Safety Administration (OSHA) to prepare a document outlining a product's composition, its hazardous ingredients, and their possible health effects. Such documents are referred to as Material Safety Data Sheets (MSDS's). A MSDS may provide some information about a particular product, but the information is often incomplete.

Suppliers usually do not warrant that the information provided in a MSDS is accurate or current, but only that it is provided in good faith. One must also recognize that the chemical components noted are of technical grade and hence contain impurities in varying amounts, the nature of which is often not known.

Problems of interpretation are present with the standard patch tests series recommended by groups such as the North American Contact Dermatitis Group (NACDG) and the ICDRG. This is a greater problem when one is testing an industrial formulation. One not only has to be concerned about false positive or negative tests, depending on whether the patch test concentration is either too high or low, but there is also the concern that you may sensitize the subject with the test. This subject has recently been reviewed by Cronin (40). The true risk of active sensitization is not known. These concerns pose a problem in testing a panel of control subjects as well if one wished to establish the subirritant concentration of an industrial chemical for patch testing.

From a practical viewpoint, if a known sensitizer is noted in a formulation's MSDS, it is wise to test the worker with the specific ingredient(s) using a standard patch test concentration. If you establish a positive response, then it is not unreasonable to accept that as the working explanation for the worker's eruption. One should then endeavor to work out a secondary preventative strategy to avoid exposure to the agent and see if the eruption improves or resolves. If it does, this would confirm the relationship of the patch test response and the worker's disease.

If this process fails, or if no known allergen is present in the formulations the worker handles, then the supplier should be approached to provide those ingredients that, in the clinician's discretion, might be possible allergens. Information is available through sources such as on-line computer data bases (i.e., Toxline® or Nioshtec®). The relative irritancy of the components to be tested may be estimated from such data. One tends to test at low concentrations (i.e., 0.01–1% in petrolatum) unless the available toxicological data suggests the chemical is a nonirritant.

Testing at low concentrations reduces the risk of active sensitization and false positive tests, but it may lead to false negative results. If continued use of a formulation repeatedly leads to an

exacerbation of the workers dermatitis then repeat patch tests at higher concentrations are indicated as the initial test result may be a false negative.

If one is unable to obtain the components of a suspect formulation, then it may be tested by preparing the entire formulation in a 0.1 or 15 concn. in petrolatum. Once again a low concentration is suggested. As before, false negative tests may occur. A minor component in the whole formulation may be the sensitizer and may be diluted to such a low concentration in the test material that the test may not elicit an observable response.

If a formulation is highly irritating, one may decide to use the open patch test method to avoid magnifying the substance's irritancy potential that could occur with an occlusive patch test. At the St. John's Hospital Contact Dermatitis Clinic, the test substance is applied either on one occasion in the clinic to a marked site on the forearm or the worker is asked to apply the substance two or three times daily over a 2-d period (41). In Toronto, we tend to apply the material only on one occasion. The presence of an inflammatory reaction at the site at 48 or 96 h is taken as evidence of a contact allergy. These tests are often hard to interpret since it is difficult to maintain contact between the chemical and the skin over a 48-h period.

If the above methods fail, one may have to rely on an exposure trial. If the eruption recurs 1–2 d after each workplace exposure, then an association can be established. It may be impossible to pin down the specific agent or combination of agents that are inducing the response. In the case of allergic contact dermatitis, one would expect that the worker could return to some alternate work assignment with either no recurrence or less exacerbation of the dermatitis. The suggestion that there may be some exacerbation is based on the observation that once a chronic response has been established, a persistent alteration in the skin's reaction to irritants may occur that is nonspecific. This has been well documented in the case of metal allergy (42–44). In these instances, one would not expect a return to work without some exacerbation, but it should be less than when exposed to the suspected allergen.

Rarely, the offending allergen may be a photoallergen. In instances when a component in a formulation is a known photoallergen, then the appropriate concentration and vehicles can be tested (45). Van Hecke has recently described a simple technique for such

tests (46). Tests with diluted formulations or formulation ingredients should be approached in the same manner as for other contactants described above.

COMMON OCCUPATIONAL CONTACT ALLERGENS

The common causes of occupational allergic contact dermatitis reported by Wilkinson et al. and Goh and Soh, as well as our own data from Toronto, are presented in Table 1 (22,23). Using the data reported by Wilkinson et al. and our own data, the relative risk of exhibiting a positive patch test response in patients with work-related allergic contact dermatitis, compared to all of the patients assessed in both clinics, has been calculated (Table 2). Differences are obvious between the three reporting sites that may reflect differences in the industrial activities of the areas, the demographic characteristics of the populations, or the interpretation of the patch test results.

Applying the criteria that the relative risk of contact sensitivity in the occupationally-related contact dermatitis cases must be increased at least twofold and that the difference must be statistically significant at the 0.05 probability level using the chi square test. Eight contactants (chromate, nickel, cobalt, thiuram, paraphenylenediamine (PPD), resin, formaldehyde, and epoxy resin) deserve special consideration as occupational allergens based on our data and that of Wilkinson et al. (23). We will limit our discussion of specific contactants to these eight.

Chromate

The most common cause of chromate allergy is cement work or the handling of construction materials containing cement or related substances. Other occupations at risk include those in the engineering trades exposed to metal and soluble oils containing chromium, tanners, milk testers, printers, and printing plate makers (47). Typically, the eruption involves the hands and forearms. A vesicular eruption on the palms mimicking dyshidrotic eczema may occur. The occasional involvement of the feet in such cases may be related to the presence of chromium in shoe leather. The disorder tends to be persistent irrespective of whether there is a change in occupation.

Table 1
Common Contact Allergens
in Cases of Occupational Allergic Contact Dermatitis

	UK, <i>n</i> = 292	Singapore, <i>n</i> = 127	Toronto, <i>n</i> = 226
Chromate	4.4	52.0	13.5
Nickel	6.5	4.0	18.9
Cobalt	2.7	4.0	17.2
Thiuram	4.1	9.4	9.5
MBT	NR ^a	9.4	1.2
MBT/mercapto mix	4.1	NR ^a	2.7
PPD	4.1	NR ^a	13.2
Resin	4.1	0.8	14.9
Formaldehyde	5.1	NR ^a	8.7
Epoxy Resin	4.1	6.3	6.8

^aNR, not reported

Table 2
Percent Positive Responses for Common Contact Allergens
in Cases of Occupational Allergic Contact Dermatitis (OACD)

	UK OACD, <i>n</i> = 292	UK All others, <i>n</i> = 992	Relative Risk ^a	Toronto OACD, <i>n</i> = 226	Toronto All others, <i>n</i> = 865	Relative Risk ^a
Chromate	4.4	2.2	2.00	13.5	4.0	3.38
Nickel	6.5	8.7	0.75	18.9	9.0	2.10
Cobalt	2.7	4.1	0.66	17.2	4.7	3.66
Thiuram	4.1	4.2	0.98	9.5	3.3	2.88
MBT ^b / mercapto mix	4.1	2.2	1.86	2.7	1.2	2.25
PPD	4.1	2.3	1.78	13.2	5.5	2.40
Resin	4.1	3.3	1.24	14.9	4.0	3.73
Formaldehyde	5.1	1.3	3.92	8.7	5.3	1.64
Epoxy Resin	4.1	1.5	2.73	6.8	1.8	3.78

^aRelative Risk was calculated by taking the ratio of the proportion of subjects with responses in the occupational group divided by the proportion of subjects with responses in the entire population tested.

^bMBT, mercaptobenzothiazole

Nickel

Nickel is one of the most common contact allergens identified in populations of patients who have been patch tested. It is predominantly a cause of contact sensitivity in women when ear piercing and the use of costume jewelry appears to account for most cases of sensitization. In the occupational setting, women frequently present with contact dermatitis, wherein a preexisting sensitivity to nickel exists, are aggravated by workplace exposure to diverse contactants, such as coinage, nickel-plated instruments, and soluble oils contaminated with nickel. In contrast, nickel sensitivity in men, prior to the recent trend in ear piercing, more likely has tended to be occupational. Metal workers, machinists, construction workers, and metal polishers are the common male occupations affected. The eruption tends to be on the hands and may mimic dyshidrotic eczema. Although occasionally a cause of recalcitrant dermatitis, it tends not to be so severe as to impair the worker and appears to have a much better prognosis in most workers than chromate sensitivity.

Cobalt

Cobalt is used with tungsten carbide to produce hard metal for cutting purposes. Workers involved in the manufacturing of this material are known to develop cobalt allergy. Cobalt is also found in electrical parts and those involved in work with electronic equipment may be sensitized. Cobalt is used in organic salts (e.g., cobalt naphthenate) as a drier in paints and varnishes, resulting in sensitization of some workers involved in the manufacturing or use of such products. Cobalt sensitivity is often found concurrent with sensitivity to nickel or chromium. It is frequently difficult to establish the source of exposure and hence the relevance of positive patch test responses to cobalt. The clinical presentation does not differ from chromium. Often, other positive patch test responses are noted in those with positive patch test responses to cobalt.

Thiuram

Along with mercaptobenzothiazole, the thiurams are the most common accelerators found in rubber in domestic as opposed to industrial use. Thiurams are commonly found in rubber gloves used

as personal protective equipment. Not surprisingly, health care workers (e.g., surgeons, nurses, and dental assistants) and individuals doing wet work (e.g., cleaners, gardeners, and housewives) tend to be present with thiuram allergy. Industrial rubber, such as coatings on cables, rubber linings in vessels, and rubber grommets, may contain thiuram, but more commonly contain unusual accelerators that account for the contact allergy. Hand dermatitis is by far the most common presentation although there may be involvement of the face and forearms. As with chromium, foot dermatitis may occur and occasionally this may be attributed to the presence of thiuram in the rubber of their shoes.

Paraphenylenediamine

PPD poses a significant risk of inducing contact allergy in individuals using PPD and PPD-related dyes in hairdressing. The sensitivity usually develops within the first two years of work and often is so disabling that a change in occupation is necessary. The dermatitis tends to have a chronic course rather like chromate allergy. The most common site of presentation is the hands. PPD derivatives are used as antioxidants in rubber and, thus, individuals handling industrial rubber may develop dermatitis of the hands related to sensitization.

Resin

Resin is ubiquitous. It is found in such diverse things as sizing in clothes, coatings on paper products, adhesives, printing inks, cutting oils, and flux for solder. Patients are usually present with hand dermatitis in the occupational setting, though occasionally airborne contact dermatitis involving the face and V of the neck may occur from exposure to soldering fume. Avoiding exposure is often associated with considerable improvement or remission of the disease, and the prognosis often good in such cases.

Formaldehyde

Formaldehyde allergy is a problem in workers manufacturing formaldehyde and products derived from formaldehyde, such as phenol formaldehyde resins and permanent press finishes such as melamine formaldehyde. Used as a mordant in the treatment of

furs, it is, along with paraphenylenediamine, a significant occupational hazard in furriers. This risk is also present in leather manufacturing. Health care workers such as pathologists, laboratory technicians, and funeral service workers are also at risk. Since formaldehyde is used as a preservative in shampoos, hairdressers are also occasionally sensitized. The dermatitis occurs at the site of contact, which is usually the hands.

Epoxy Resin

These materials are widely used in industry as adhesives and electrical insulators. Workers in the electrical industry involved in such things as the manufacture of printed circuit boards and the installation of cathodic insulation may experience difficulty. The use of such materials in the aircraft manufacturing industry, fiberglass work (e.g. auto body work and hand lay-up boat manufacturing), and furniture manufacturing also poses a risk. The eruption involves the hands and forearms and frequently the eyelids. The process tends to remit with avoidance of further exposure even if the process becomes chronic.

OCCUPATIONS ASSOCIATED WITH ALLERGIC CONTACT DERMATITIS

In a review of 226 cases of occupational allergic contact dermatitis seen in Toronto, the proportion of workers from several classes of industries presenting allergic contact dermatitis is noted in Table 3, along with similar data reported from the UK (23). As mentioned above, it is clear that the industrial mix in a given area has an influence on the generation of cases of contact dermatitis. The Canadian and English data cited illustrate this point. Workers presenting with the disease tend to come from a wide variety of industries.

AGE AND SEX DIFFERENCES

Allergic contact sensitivity to common allergens tends to increase with age (48). In our experience, allergic contact dermatitis has tended to be more common than irritant contact dermatitis in female workers in Toronto.

Table 3
Percentage of Cases
of Occupational Allergic Contact Dermatitis in Given Industries

Industry	UK, <i>n</i> = 209	Toronto, <i>n</i> = 226
Engineering	10	7
Furniture	36	5
Rubber, Plastics, Foam, Chemical	15	7
Paper, Printing	7	4
Agriculture	2	1
Hairdressing	2	13
Electrical, Electronic	7	1
Construction, Maintenance	4	10
Other		
Service—Wet	4	—
Service—Dry	8	—
Health Care/Dental	—	11
Laborer	—	23
Aircraft/Auto	—	3
Textile	—	3
Miscellaneous	5	12

LOCATION OF ERUPTION

A review of 460 allergic contact dermatitis cases that we have evaluated reveals differences in the topographical distribution of the eruption in cases that were occupational (Table 4). Work-related disease has tended to be on the hands and arms, not on the face, eyelids, or neck.

MANAGEMENT

In the case of an individual with acute allergic contact dermatitis the approach is, in principle, simple. One instructs the worker to avoid further contact, treat the local eruption with compresses and topical steroids, and anticipates complete resolution of the disease. In cases with extensive or severe involvement, or where an auto-sensitization dermatitis has developed, oral steroid therapy at a dose of 1 mg/kg body wt of prednisone for 7–10 d is indicated follow-

Table 4
Location of Eruption
in Occupational and Nonoccupational Allergic Contact Dermatitis

Location	Occupational, <i>n</i> = 226	Nonoccupational <i>n</i> = 234	<i>p</i> value
Hands	88.5%	36.2%	0.000
Arms	17.7%	6.8%	0.000
Face	8.0%	38.0%	0.000
Eyelids	3.0%	12.4%	0.000
Neck	3.1%	8.1%	0.020
Legs	1.8%	3.0%	0.391
Feet	5.8%	6.0%	0.916
Trunk	1.8%	3.9%	0.179

ing which the dose is tapered over a further 7–10 d. Certainly there are instances when the problem continues to recur because of an inability to identify the offending contactant or the source of exposure which, needless to say, significantly complicated management of the problem.

In workers with chronic occupational allergic contact dermatitis, the approach is different. The therapist must set realistic expectations from the first interaction with the worker. One should not promise a cure, only the possibility of improvement with avoidance of a specific allergen, if it can be determined. Attention must be paid to minimizing exposure to occupational and leisure time irritants since these will tend to perpetuate the dermatitis even if the offending allergen is avoided.

The effective use of personal protective equipment (i.e., gloves, gauntlets, and aprons) or the interposition of engineering controls to minimize skin contact may allow some workers to continue to work in an environment when the allergen is used without further difficulty. More commonly, once sensitization has occurred, continued work with the offending substance is associated with intermittent bouts of exacerbation of the dermatitis.

Topical steroids should be used sparingly and intermittently since frequent use of potent steroids may result in skin atrophy and impair the worker's capacity to do physical work with their hands. Oral or intravenous steroid therapy should be avoided since it will usually only afford temporary relief and the long-term side effects may pose a significant risk to the patient's general health.

PROGNOSIS

The prognosis in acute dermatitis is excellent; in chronic occupational allergic contact dermatitis, it is poor. The disability is usually one that the worker has to accept. With encouragement, workers can often remain on the job while taking precautions to avoid exposure to the allergen and endeavoring to minimize physical and chemical injury to their skin. In short, they must come to terms with a certain level of disease. Many cannot. In these instances, they often suffer significant social losses owing to unemployment and less than compensatory disability benefits (49).

PREVENTION

The provision of advice to workers, before they enter trades where there is exposure to allergens, should facilitate primary prevention of occupational allergic contact dermatitis. A past history of contact allergy to several environmental contactants would suggest that the worker may be at greater risk of developing allergic contact dermatitis (50). A history of atopy does not predispose one to occupational allergic contact dermatitis, though once having acquired contact dermatitis, those with a history of atopic dermatitis tend not to be as likely to resolve it (51).

Patch tests should not be performed on prospective workers prior to job placement. This is because of the risk of active sensitization through the test procedure. Close observation of new workers for the presence of contact dermatitis in the first week of employment will allow the identification of those workers with preexisting allergic contact dermatitis to chemicals. In these instances, patch tests to confirm allergic contact sensitivity is justified.

Predictive tests in animals, such as the Landsteiner-Draize Test, Guinea Pig Maximization Test, and others, may give an indication of a chemical's sensitization potential for humans (52,53). Human data, such as the results of the Human Maximization Test, the Draize Test, or the Shelanski-Shelanski Test, may give even more applicable human data (54). When one has such human or animal data combined with information regarding usage experience with comparable chemicals also tested, then a reasonable idea about the risk of developing allergic contact dermatitis in a usage situation

can be predicted. The best information is documented past experience with the use of the chemical in a situation comparable to the usage situation envisaged.

Depending on the level of practical risk sensitization of workers in the use situation (i.e., the hazard), prevention may simply involve the use of personal protective equipment (i.e., gloves, aprons, shoe covers, and goggles) or, if the hazard is great, engineering controls may be needed to eliminate skin contact entirely if occupational allergic contact dermatitis is to be avoided. For any such program to work, it must be coupled with a program of worker education. As a general rule, barrier creams have proven ineffective as a preventive measure except when they are used as an adjunct to other methods of controlling cutaneous exposure.

REFERENCES

1. Lane, G. (1942), *JAMA* 118, 613-615.
2. National Institute for Allergic and Immunologic Disease Task Force (1979), United States Department of Health, Education, and Welfare, NIH Publication 79-387, p. 395.
3. Odland, G. (1971), *The Skin: A Description of the External Organ and its Common Afflictions*, University of Washington Press, Seattle, p. 88.
4. Mathias, C. G. T. (1985), *Arch. Dermatol.* 121, 332-334.
5. Keil, J. and Shmumes, E. (1983), *Arch. Dermatol.* 119, 650-654.
6. Williamson, D. M. (1982), *Practitioner* 226, 1285-1290.
7. Meding, B. and Swanbeck, G. (1987), *Br. J. Dermatol.* 116, 627-634.
8. Kavli, G. and Forde, O. (1984), *Contact Dermatitis* 10, 174-177.
9. Coenraads, P., Nater, J., and van der Lende, R. (1983), *Clin. Exp. Dermatol.* 8, 495-503.
10. Lantinga, H., Nater, J. P., and Coenraads, P. J. (1984), *Contact Dermatitis* 10, 135-139.
11. Wahlberg, J. E. (1969), *Berufsdermatosen* 17, 184-198.
12. Hogberg, M. and Wahlberg, J. E. (1980), *Contact Dermatitis* 6, 100-106.
13. Varigos, G. A. and Dunt, D. R. (1981), *Contact Dermatitis* 7, 105-110.
14. Stovall, G. K., Levin, L., and Oler, J. (1983), *J. Occup. Med.* 25, 871-878.
15. Estlander, T., Rajaniceir, R., and Jolanki, R. (1984), *Contact Dermatitis* 10, 201-205.

16. Lammintausta, K., Kalimo, K., and Havu, N. (1982), *Contact Dermatitis* 8, 84-90.
17. Lammintausta, K., Kalimo, K., and Amta, S. (1982), *Contact Dermatitis* 12, 327-333.
18. Mathur, N. K., Mathur, A., and Banerjee, K. (1985), *Contact Dermatitis* 12, 38-41.
19. Ligo, R. N. and James, R. B. (1974), *Cutis* 13, 527.
20. Adams, R. (1986), *Clin. Rev. Aller.* 4, 323-338.
21. Jordan, W. (1974), *Arch. Dermatol.* 110, 567-569.
22. Goh, C. L. and Soh, S. D. (1984), *Contact Dermatitis* 11, 288-293.
23. Wilkinson, D. S., Budden, M. G., and Hambly, E. M. (1980), *Contact Dermatitis* 6, 11-17.
24. Hjorth, N. and Fregert, S. (1979), *Textbook of Dermatology*, 3rd ed., (Rook, A., Wilkinson, D., and Ebling, F., eds.), Blackwell, London, pp. 385-392.
25. Fisher, A. A. (1986), *Contact Dermatitis*, 3rd ed., Lea and Febiger, Philadelphia, PA, pp. 77-99.
26. Adams, R. M. (1983), *Occupational Skin Disease*, Grune and Stratton, New York, NY, pp. 16-18.
27. Nethercott, J. R. *Occupational Medicine*, (LeDou, J., ed.), Lange Medical Publications (in press), Los Altos, California.
28. National Institute for Allergic and Immunologic Disease Task Force (1979), United States Department of Health, Education, and Welfare, NIH Publication 79-387, p. 400.
29. Hannuksela, M. (1979), *Allergy* 34, 5-10.
30. Fregert, S. (1981), *Manual of Contact Dermatitis*, Year Book Medical Publishers, Chicago, IL.
31. Cronin, E. (1980), *Contact Dermatitis*, Churchill Livingstone, New York, NY, pp. 1-20.
32. Adams, R. M. (1983), *Occupational Skin Disease*, Grune and Stratton, New York, NY, pp. 136-156.
33. Fisher, A. A. (1986), *Contact Dermatitis*, 3rd ed., Lea and Febiger, Philadelphia, PA, pp. 9-29.
34. Hjorth, N. and Fregert, S. (1979), *Textbook of Dermatology*, 3rd ed., (Rook, A., Wilkinson, D., and Ebling, F., eds.), Blackwell, London, pp. 429, 430.
35. Adams, R. M. (1983), *Occupational Skin Disease*, Grune and Stratton, New York, NY, pp. 16-18.
36. Hindson, C. (1985), *Essentials of Industrial Dermatology*, (Griffiths, W. and Wilkinson, D., eds.), Blackwell, Oxford, pp. 28-31.
37. Mitchell, J. (1975), *Contact Dermatitis* 1, 193, 194.
38. Maibach, H. (1981), *New Trends in Allergy*, (Ring, J. and Burg, G., eds.), Springer-Verlag, New York, NY, pp. 208-221.
39. Mitchell, J. C. (1977), *Contact Dermatitis* 3, 315-320.

40. Cronin, E. (1980), *Contact Dermatitis*, Churchill Livingstone, New York, NY, pp. 15,16.
41. Cronin, E. (1980), *Contact Dermatitis*, Churchill Livingstone, New York, NY, p.17.
42. Christensen, O. B. (1982), *Contact Dermatitis* 8, 7-15.
43. Doooms-Goosens, A., Ceuterick, A., Vanmaele, N., and Degreef, H. (1980), *Dermatologica* 160, 249-260.
44. Burrows, D. (1984), *Int. J. Dermatol.* 23, 215-220.
45. Cronin, E. (1980), *Contact Dermatitis*, Churchill Livingstone, New York, NY, pp. 8,9.
46. van Hecke, E. (1982), *Contact Dermatitis*, 8, 363-372.
47. Cronin, E. (1980), *Contact Dermatitis*, Churchill Livingstone, New York, NY, pp. 293-311.
48. Coenraads, P. J., Bleumink, E., and Nater, J. P. (1975), *Contact Dermatitis* 1, 377-381.
49. Nethercott, J. R. and Gallant, C. (1986), *Occupational Medicine: State of the Art Reviews* 1, 199-203.
50. Moss, C., Friedmann, P. S., Shuster, S., and Simpson, J. (1985), *Clin. Exp. Immunol.* 61, 232-241.
51. Rystedt, I. (1985), *Contact Dermatitis* 12, 247-254.
52. Magnusson, B. and Kligman, A. (1970), *Allergic Contact Dermatitis in the Guinea Pig*, Charles C. Thomas, Springfield, IL.
53. Marzulli, F. and Maibach, H. (eds) (1977), *Dermatotoxicology and Pharmacology*, Hemisphere, Washington, DC.
54. Marzulli, F. and Maibach, H. (1986), *Contact Dermatitis*, 3rd ed., (Fisher, A. A., ed.), Lea and Febiger, Philadelphia, PA, pp. 30-45.

9 - MALADIES DENTAIRES D'ORIGINE PROFESSIONNELLE

Dans l'alimentation les poussières organiques peuvent tacher les dents ou contribuer à la carie. Les poussières d'os, de farine, de tabac, de cellulose etc... peuvent tacher les dents, faire apparaître des pigmentations gingivales, causer des abrasions, générer des calculs salivaires et provoquer des saignements.

On rapporte une prévalence élevée de caries dentaires chez les travailleurs des raffineries de sucre, des pâtisseries et des établissements de confection de bonbons et de chocolats. Le sucre tend à se déposer le long des surfaces gingivales de la couronne dentaire et à stagner, induisant ainsi une fermentation anormale et avec l'aide des bactéries, une production d'acide.

Prévention

Les moyens de prévention suivants sont recommandés :

- contrôle des poussières organiques par les moyens technologiques
- hygiène dentaire individuelle
- information sur les risques de problèmes dentaires
- surveillance médicale et dentaire dans les milieux où l'évaluation environnementale démontre des risques.

Occupational Diseases of Teeth

B. N. GUPTA

Industrial Toxicology Research Centre, Lucknow, India

Summary

Occupational diseases of the teeth have, in general, received scant attention. The chief cause of this is lack of awareness among occupational physicians. Exposure to various chemical substances is one of the causes of occupation-related dental disorders. Physical and biological factors also contribute. The combination of these factors plus poor dental hygiene aggravates the condition. The present article aims to focus the attention of occupational physicians towards this important problem.

Introduction

Teeth are affected in a number of occupations. In fact, dental manifestations may be the very first signs of an occupational disease and their early detection may help in preventing such diseases. It thus becomes essential for dental surgeons, general practitioners and specially industrial physicians to acquire a good knowledge and experience of the dental manifestations of occupational diseases. This will help them to eliminate the chances of erroneous diagnosis and in screening cases of occupational origin to prevent further hazards.

Workers may develop disorders of teeth because of physical factors or exposure to chemical substances, organic or inorganic, specific to their occupation. Chemical substances are the principal causes of occupational diseases. With the considerable expansion of chemical industries producing many synthetic formulations there should be a vigilant check on the workers for any systemic or dental ill effects. Apart from the chemical agents, physical factors like radium, X-ray and biological factors produce ill effects on workers.

Dust

Dust of abrasive quality such as cement or sand, may collect on the occlusal surfaces of the teeth and produce generalized abrasion. Such a condition is usually found among cement and sand workers, grinders, stone cutters and miners etc. Peterson and Henmar¹ reported 100 per cent prevalence of dental abrasion among workers in the Danish granite industry. Similarly Enbom *et al.*² found a statistically significant higher degree of occlusal wear among miners than among white collar workers in Sweden.

Organic dusts

Bone, celluloid, sawdust, flour, tobacco etc. may produce staining of teeth, pigmentation of gingivae, generalized abrasion, calculus, gingivo-stomatitis and haemorrhage in workers exposed to these dusts.

A high prevalence of tooth decay has been reported among workers like sugar refiners, bakers and candy makers who are exposed to sugar dust. Sugar tends to deposit itself along the labial gingival surfaces of the crown where it stagnates and induces abnormal fermentation and, with the aid of bacteria, acid production. The highest prevalence of caries is reported among sugar bakers. The historical paper of Gelbier³ has summarized the provision of some types of dental care facilities in chocolate factories in the early twentieth century.

Inorganic dusts

METALS

Metallic poisoning used to be confined to mercury, lead and arsenic but with the expansion of industrial processes more and more metals are being used and the worker is now exposed to the hazards from them. Though some pure metals may be harmless, their compounds and particularly their acid salts are toxic.

Copper produces greenish stains on the teeth due to inhalation of the dust. It is also reported to occur among musicians who use brass instruments which impinge on the front teeth, which are affected by the copper in the alloy. The colour is due to the formation of the carbonate or subacetate of copper.

Nickel reproduces green stains on the teeth of the workers because of inhalation of the dust and as a result of the action of the salivary contents on the metal.

Workers in iron mines develop a fine black line on the teeth approximately 1 mm or so above the gingival line and in crevices. Sometimes the black pigmentation is present over a rather large surface. The stain usually recurs after its removal. It is interesting to note that the teeth of individuals with such stains tend to show a reduced incidence of caries. Iron may be inhaled in the form of dust or fumes in the processing of steel rods with hydrochloric acid.

Bismuth handlers and dusting powder makers, who are constantly inhaling dust, develop a black or purplish pigmentation round the gingival margin due to the precipitation of sulphide. A similar patch of discoloration is often produced on the mucosa of the cheek in the part that is resting against the gingivae.

Air contaminated with chromic acid mist or with the dust from chromates or bichromates of potassium and sodium is the principal source of exposure in industry. Exposure to these substances occurs among chromium platers, colour workers, calico printers, photographers, litho-etchers, chrome tanners and steel workers. Exposure to chromic acid and chromates and bichromates may produce blue pigmentation of gingivae and oral mucosa, gingivostomatitis, necrosis of bone and ulceration of gums and oral tissue. Gomes⁴ reported that more than 50 per cent of the workers engaged in electroplating in Brazil had dental disorders caused by high chromium content in the work environment.

Lead produces the well known blue line on gums, sometimes called the 'Burtonian line' and described by Grisolle⁵ and Burton⁶. It consists of fine granules of pigment arranged in the form of a dark blue stippled line within the tissue of the gum and about a millimetre from the margin. It is more marked round teeth having infected gingival troughs and may occasionally be found on the mucosa of the cheek opposite such teeth. The line is more frequently seen on the mandibular gum than on the

maxillary and in the incisor region than in the molar. Although this is not a disease of the teeth it has been mentioned here because the stain does not occur if there are no teeth. The stain is a precipitate of lead sulphide caused by the action of hydrogen sulphide upon the lead salts in the circulation.

Despite its lying within the tissues, careful cleaning of the mouth and teeth removes the pigment. The stain is indicative of absorption and not of intoxication. Its intensity and size provide a rough guide to the duration and severity of exposure to lead. It occurs in plumbers, and compositors, through inhalation of dust and from the fumes from lead battery casings. Workers involved in the manufacture of hair dyes and cosmetics containing lead may also become affected.

Localized argyria may result from exposure to metallic silver during industrial processing of the metal. It gives an appearance similar to that of tattoo work.

Manganese is used in the manufacture of iron and steel, organic chemicals and dry cells, in photography, in the fertilizer industry, paints and ceramics, glass industry, dyeing, printing and bleaching processes, in the preservation of wood and in disinfecting and oxidizing processes apart from being used in various mining operations. Sometimes a black deposit of hydrated manganese dioxide may be formed on the teeth when the condition in the mouth predisposes its formation.

Workers are exposed to cadmium during various operations in zinc smelting plants, rolling mills, nickel-cadmium battery factories, electrical industry, automotive engines, aircraft engines, marine engines, electroplating, welding and soldering processes, manufacture of glass, dentistry and photography. The workers in these industries may show some changes in their teeth because of exposure to cadmium. The workers may get yellow or gold-brown stains particularly on the labial surfaces of the front teeth, and these stains are most intense on the neck. Calculus is also stained. A staining of calculus (i.e. the hard deposit on teeth) rather than the teeth themselves can be removed by scaling as the stain is simply chipped away and lost with the calculus when the latter comes off. However, staining of the underlying tooth tissue might still remain. This pigmentation is a 'danger' sign of toxic absorption.

Yellow staining of teeth is sometimes seen among workers exposed to tin. It is due to a deposit of tin sulphide. In printing presses the lino type metal is an alloy of 85 per cent lead, 12 per cent antimony and 3 per cent tin. It is kept in a molten state in a container on the machine. The metal fumes come out and may be inhaled by the workers. Workers in tin mines are also exposed to stannic oxide dust. The staining presumably occurs when there is a pre-carious or early carious lesion present and non-carious enamel shows no colour changes.

Striations are produced in the dentine of the incisors of rats which have been fed with diets containing strontium. No authentic report of the effect of strontium on human teeth is available.

Workers in mercury mining, the manufacture of thermometers, barometers etc., electrical industry, pharmaceutical industry, photoengraving, manufacture of felt hats, identification of fingerprints etc. are exposed to the hazards of mercury poisoning. Since mercury evaporates even at an ordinary temperature it contaminates the air during various industrial processes. Although it can be absorbed through skin, poisoning occurs mainly through the respiratory tract. Apart from producing

symptoms like salivation, stomatitis, tremors, nervousness, irritability, depression, insomnia, cachexia etc., it also affects the teeth and gums. The gums become tender, swollen, red, ulcerated and bleed readily and the teeth become loose. Kussmaul⁷ reporting the pitiable condition of mirror makers found almost every male adult to be without a single tooth in Furth and Nuremberg. This may have been because of poor dental services in the nineteenth century. A mercurial line on the gums is now hardly ever seen. It usually resembles the blue line due to absorption of lead but is sometimes dark brown. Vigliani *et al.*⁸ reported gingivitis and loss of teeth among workers in the felt hat industry exposed to mercury.

Dentists are also subject to danger from mercury⁹.

NON-METALS

Fluorine, hydrofluoric acid and silicon fluoride are used in the superphosphate industry, during the manufacture of phosphorus and in the production of hydrogen peroxide. Fluorine or the vapours of hydrofluoric acid, if inhaled, cause a burning pain in the chest, cough and even hemoptysis. The ultimate result is slow ulceration of the gums, nasal mucosa, larynx, bronchi and conjunctivae.

Fluorspar or fluorite is calcium fluoride and is used in the manufacture of steel, ceramics and hydrofluoric acid. Fluorapatite, a fluorine compound, is evolved as a by-product in the manufacture of super phosphate. Cryolite (sodium aluminium fluoride) is used as a flux in metallurgy and contains as much as 54 per cent fluorine. Crushing, grinding, grading, drying and all handling of it produce dust and all workers in the factory are exposed to its hazards. Apart from leading to fluorosis of bones and ligaments, anaemia and other toxic signs and symptoms the workers are likely to develop fluorosis of teeth in their formative stage. The condition consists of greyish and chalky-white blotches and streaks scattered over the entire tooth surface involving all the teeth. The surfaces of some teeth are dotted with minute, irregular and shallow pits in the enamel. Sometimes there is incomplete calcification of the cusp tips. In about 40 per cent of cases this general condition is aggravated by discoloration of the enamel from light brown to almost black. The essential malformation is in the cementing substance between the enamel rods on the outermost part of the surface of the enamel. Evidently fluorine compounds produce a direct local action on enamel-forming cells. Lezovic and Arnost¹⁰ reported four cases of occupational fluorosis in individuals who had been working in an aluminium plant for periods of up to 12 years. Their teeth contained unusually high fluorine levels. It may be because of ionic interchange at the tooth surface in these workers. Such ionic activity occurs on the enamel surface, for example, during periods of dental decay and subsequent re-mineralization of the teeth. During the latter phase, the decay process is reversed.

DENTAL FLUOROSIS IN THE OFFSPRING OF THE WORKERS

It is to be noted that mottling of the dental enamel can occur only when the teeth are subjected to fluorine compounds during their development. In case of permanent teeth such exposure must take place before the age of nine. It follows that adults absorbing fluorine compounds during their work in a factory cannot have alterations in their dental enamel. However, it was noted that the children of female cryolite workers in Copenhagen showed mottling of the teeth. These cases show that fluorine

compounds are excreted in the milk of the women after their exposure to cryolite dust. This seems so far to be the only authentic example of transmission of an occupational disease to the offspring of a factory worker. The exact mechanism of such a phenomenon needs elucidation.

Workers are exposed to phosphorus in the manufacture of matches, rat-poison, fireworks, smoke screens, marker shells, tracer bullets, bombs, hand grenades, phosphor-bronze, cellulose, dyes, soaps, fertilizers, plasticizers and insecticides, and in petroleum refineries, paper industry, printing and rust-proofing of steel are exposed to its hazards.

The first symptom of phosphorus poisoning is toothache which usually begins in a tooth already affected with caries. A dull red spot on the buccal mucosa is seen at this stage and there is usually a sinus surrounded by dull red mucosa leading to a cavity underneath. Sequestra up to one centimetre in diameter may be found. They are both osteoporotic and carious. A major report on the problems of phosphorus workers was produced in 1899 by a dentist George Cunningham and two of his colleagues. Therein they described a condition called 'phossy jaw'. Among other recommendations they stressed the need to appoint a dentist in each factory. As a result, Bryant and May started a two-chair surgery, probably the first of its kind by way of an industrial dental service at their London factory¹¹. Ward¹² reported 18 cases of phosphorus necrosis among workers engaged in the manufacture of fireworks. Hughes *et al.*¹³ reported 10 typical cases of phosphorus necrosis of the jaw.

Teeth are known to remain unaffected by arsenic. However, oral mucous membrane may become intensely inflamed and severe gingivitis with pain may occur. Local contact with arsenic trioxide often produces ulceration of the gums. Frost¹⁴ has described the harmful effects among industrial workers of exposure to arsenic. Hairdressers in the thirties and forties suffered from arsenic toxicity because of their practice of holding hair grips with their teeth.

Citric acid, tartaric acid, hydrochloric acid, nitric acid and sulphuric acid etc. affect the teeth of the workers exposed to these acid fumes. Decalcification of enamel and dentine occurs following exposure to acid among workers in factories manufacturing explosives or acid dippers. The acid fumes deposited on the exposed portions of the teeth react with the enamel and decalcification results. The earliest reaction consists of a superficial decalcification of the enamel of the labial surface of the tooth which is exposed the most. Mastication and tooth brushing wear off the partially decalcified areas and produce flat smooth surfaces. The degree of erosion increases with the length of period of employment. The eroded surface is smooth and polished and never pitted. When the enamel has been destroyed, the dentine is attacked and there is brown or black discoloration of the affected teeth but they retain their polish. While the erosion is taking place the pulp chamber shrinks and the condition is painless except in rare cases where the erosion is so rapid that bacterial invasion of the pulp cavity occurs causing abscess formation. Barsotti *et al.*¹⁵ reported that 19.2 per cent of workers exposed to tartaric acid showed erosion of the incisive and canine teeth. Malcolm and Paul¹⁶ in a study of workers in the storage battery industry reported that workers exposed to acid mist were found to have erosion of the incisor teeth. Gamble¹⁷ in a

study of acid battery workers found that the ratio of observed to expected prevalence of teeth etching and erosion was about four times greater in the high acid-exposure group. The earliest case of etching occurred after exposure for 4 months to an estimated average exposure of 0.23 mg sulphuric acid/m³.

Physical Factors

Occupational injuries may give rise to concussion, loosening or fracture of teeth.

Modifications of the teeth by abrasion occur among shoe makers, upholsterers, glass blowers, dress designers, dress makers and seamstresses. They result from holding nails, tacks, needles, glass tubes and thread reinforced by metals between their teeth. The cobbler holds a ready supply of nails – 30 or so – in his mouth and serves them out from his teeth, and the upholsterer and sofa maker does the same with tacks. Nurses using hairgrips in the same manner sometimes develop changes in their teeth.

Musicians, especially the wind instrument players, develop dental problems. These are mainly the problems of 'embouchure'. The way in which the lips and mouth are applied in the blowing of a wind instrument is known as 'embouchure'. The presence of dental defects can affect the playing of the instruments. The dental problems among wind instrument players have been studied¹⁸⁻²².

Teeth of people who have received harmful doses of X-ray radiations like X-ray technicians, radiographers, research workers and watch dial painters (who lick their brushes) are sometimes affected. Way back in 1925 Hoffman²³ reported four cases in which necrosis of the teeth and jawbones had occurred after the practice of pointing the paint brush with radium on it. The damage by radiation may not appear for several years. The gingivae become inflamed, ulcerated and painful and a foul breath may be present. This may be followed by gingival recession, periodontitis and damage to alveolar bone. The teeth become loose and show resorption of the root. In the later stages, osteomyelitis, osteonecrosis and osteosclerosis of the jaw accompanied by loss of teeth and the formation of sequestra occur. The most common manifestation of radiation injury is a typical destruction of tooth substance resembling dental caries at the cemento-enamel junction and sometimes called 'radiation caries'. Teeth often seem brittle, and pieces of the enamel may fracture away from the tooth. Recent experiences with radiotherapy of malignant diseases²⁴⁻²⁶ have shown that excessive dosage of radiation has severe adverse effects on the teeth.

Increased atmospheric pressure may produce bleeding from gingivae among people working in compressed air chambers. The same complaint may be noticed among aviators due to decreased atmospheric pressure. During the Second World War dental pain was observed in some of the personnel of aircrews flying at high altitude or entering the low pressure chamber. The cause of the pain has been attributed to air embolism being present in the dental pulp. Pain is particularly liable to occur if there is already an inflammatory condition of the pulp.

Effect of Adverse Environmental Factors on Rat Incisors

Comparison between the histology and chemical composition of the incisors of rats acclimatized for 18-24 weeks to cold, neutral or hot atmospheres, at various

barometric pressures showed interesting results. Cold by itself induced negligible histological changes, but altitude (750 or 380 mmHg) produced changes in the mesenchyma of the teeth. These were made severe by superimposed cold (3°C), but superimposed heat (36°C) counteracted some of these effects. The latter group, however, had ectodermal changes. Chemical studies revealed significantly reduced concentrations of calcium, phosphate and magnesium in the teeth of the altitude- and heat-exposed rats. The teeth of rats are continuously growing and this process is similar to the unerupted human tooth formation, and therefore the effects observed in the rats in this experiment may presumably be seen among children if they are exposed to the same conditions.

Because of physiological strains in certain occupations people may develop bruxism or bruxomania, i.e. the habit of constantly grinding their teeth. Athletes engaged in physical activities often develop this habit. The exact reason for this is unknown. Occupations in which the work has to be near precise such as that of the watch maker are likely to cause bruxism. When the habit is firmly established severe scarring or attrition of the teeth may occur.

Importance of oral hygiene

Neglect of oral hygiene predisposes the teeth to the development of occupational dental diseases and aggravation of the disease once it occurs. The presence of the aetiological agent alone is not enough to cause dental diseases. The general and oral health of the patient are equally important.

The scope of this paper does not include a consideration of the treatment of various occupational dental disorders. However, there is no denying that prevention of their occurrence is better than a treatment once they occur. Prevention can be effected by proper working conditions and observation of strict oral hygiene. Since oral hygiene is a matter of habit it should be inculcated in early childhood. So that a person is well guarded against any occupational hazard in the course of his employment. Moreover, the training for a particular occupation should include attention to the general health of the worker and particularly to those parts of the body which are exposed to dental occupational hazards. Adequate provision for industrial health should aim at prevention, if possible, or an early recognition and treatment of dental occupational diseases. L'Epée²⁷ has stressed the importance of oral and dental examination as part of the occupational health service.

More studies of occupational diseases of teeth should be conducted in order to check or confirm previous reports and to discover possible manifestations arising among workers in new industries. It is essential for all concerned to have an epidemiological knowledge of the state of oral health of the workers, especially if there are conditions in the industry likely to cause dental disorders²⁸.

REFERENCES

- Peterson PE, Henmar P. Oral conditions among workers in the Danish granite industry. *Scand J Work, Environ Health* 1988; 14: 328.
- Enbom L, Magnusson T, Wall G. Occlusal wear in miners. *Swed Dent J* 1986; 10: 165.
- Gelbier S. Dental health and the chocolate factory. *Occas News Letter, Dental Historian* 1986; 12: 17.
- Gomes ER. Incidence of chromium induced lesions among electroplating workers in Brazil. *Indust Med* 1972; 41: 21.
- Grisolle A. Recherches sur quelquesuns des accidents cerebraux produits par les preparations saturnines, Paris, 1836. Quoted in: Hunter D, ed. *The diseases of occupations*, 4th ed., Aylesbury: Hazell Watson & Viney Ltd., 1969.
- Burton H. *Lancet* 1840; 1: 661. Quoted in Hunter D, ed. *The diseases of occupations* 4th ed., Aylesbury: Hazell Watson & Viney Ltd., 1969.
- Kussmaul A. Untersuchungen uber dem constitutionellen Mercurialismus, Wurzburg; 1861. Quoted in: Hunter D, ed. *The diseases of occupations* 4th ed., Aylesbury: Hazell Watson & Viney Ltd., 1969.
- Vigliani EC, Baldi G, Zurlo N. Chronic mercurialism in the felt hat industry. *Med Lav* 1953; 44: 161.
- Gelbier S, Ingram J. Possible foetotoxic effects of mercury vapour: a case report. *Public Health* 1989; 103: 35.
- Lezovic J, Arnost L. Occupational skeletal fluorosis. *Fluoride Quarterly Reports* 1969; 2: 120.
- Davis HC. George Cunningham; the man and his message. *Br Dent J* 1969; 127: 527.
- Ward EF. Phosphorus necrosis in the manufacture of fireworks and in the preparation of phosphorus. *Bulletin of the U.S. Bureau of Labor Statistics* 1926; 405: 1.
- Hughes JPW, Baron R, Buckland DH et al. Phosphorus necrosis of the jaw - A present day study with clinical and biochemical study. *Br J Ind Med* 1962; 19: 83.
- Frost DV. Arsenicals in biology - Retrospect and prospect. *Federation Proceedings* 1967; 26: 194.
- Barsotti M, Sassi C, Ghetti G. Health hazards in a tartaric acid factory. *Medicine Del Lavoro*, 1954; 45: 239.
- Malcolm D, Paul E. Erosion of teeth due to sulphuric acid in the battery industry. *Br J Indust Med* 1961; 18: 63.
- Gamble J, Jones W, Hancock J, Meckstroth RL. Epidemiological - environmental study of lead acid battery workers. III. Chronic effects of sulfuric acid on the respiratory system and teeth. *Environ Res* 1984; 35: 30.
- Porter MM. Problems of embouchure comfort: A matter for dental concern. *Scientific and Educational Bulletin of International College of Dentists*, Berkley, California, U.S.A. 1971; 1.
- Porter MM. The embouchure and dental hazards of wind instrumentalists. *Proc R Soc Med* 1973; 66: 1075.
- Corcoran DF. Dental problems in musicians. *Journal of Irish Dental Association* 1985; 31: 4.
- Farkas P. Medical problems of wind players: a musician's perspective. *Cleve Clin Q* 1986; 53: 33.
- Fine L. Dental problems in the wind instrumentalists. *Cleve Clin Q* 1986; 53: 3.
- Hoffman FL. Radium (Mesothorium) necrosis. *JAMA* 1925; 13: 961.
- Ansell G. *Radiology in clinical toxicology*. Published by London: Butterworth & Co. Ltd., 1974, 146.
- Dury DC, Robert MW, Miser JS, Folio J. Dental root agenesis secondary to irradiation therapy in a case of rhabdomyosarcoma of middle ear. *Oral Surg Oral Med Oral Pathol* 1984; 57: 595.
- Maguire A, Murray JJ, Craft AW, Kernahan J, Welbury RR. Radiological features of the long-term effects from treatment of malignant disease in child hood. *Br Dental J* 1987; 162: 99.
- L'Epée P. The value of oral and dental examinations as part of the occupational medicine service. *Archives Des Maladies Professionnelles* 1969; 30: 428.
- Lesquoy H. Diseases of the teeth of occupational origin. *Faculte de medicine, Université de Strasbourg, Strasbourg, France*, 1983; 82.

compounds are excreted in the milk of the women after their exposure to cryolite dust. This seems so far to be the only authentic example of transmission of an occupational disease to the offspring of a factory worker. The exact mechanism of such a phenomenon needs elucidation.

Workers are exposed to phosphorus in the manufacture of matches, rat-poison, fireworks, smoke screens, marker shells, tracer bullets, bombs, hand grenades, phosphor-bronze, cellulose, dyes, soaps, fertilizers, plasticizers and insecticides, and in petroleum refineries, paper industry, printing and rust-proofing of steel are exposed to its hazards.

The first symptom of phosphorus poisoning is toothache which usually begins in a tooth already affected with caries. A dull red spot on the buccal mucosa is seen at this stage and there is usually a sinus surrounded by dull red mucosa leading to a cavity underneath. Sequestra up to one centimetre in diameter may be found. They are both osteoporotic and carious. A major report on the problems of phosphorus workers was produced in 1899 by a dentist George Cunningham and two of his colleagues. Therein they described a condition called 'phossy jaw'. Among other recommendations they stressed the need to appoint a dentist in each factory. As a result, Bryant and May started a two-chair surgery, probably the first of its kind by way of an industrial dental service at their London factory¹¹. Ward¹² reported 18 cases of phosphorus necrosis among workers engaged in the manufacture of fireworks. Hughes *et al.*¹³ reported 10 typical cases of phosphorus necrosis of the jaw.

Teeth are known to remain unaffected by arsenic. However, oral mucous membrane may become intensely inflamed and severe gingivitis with pain may occur. Local contact with arsenic trioxide often produces ulceration of the gums. Frost¹⁴ has described the harmful effects among industrial workers of exposure to arsenic. Hairdressers in the thirties and forties suffered from arsenic toxicity because of their practice of holding hair grips with their teeth.

Citric acid, tartaric acid, hydrochloric acid, nitric acid and sulphuric acid etc. affect the teeth of the workers exposed to these acid fumes. Decalcification of enamel and dentine occurs following exposure to acid among workers in factories manufacturing explosives or acid dippers. The acid fumes deposited on the exposed portions of the teeth react with the enamel and decalcification results. The earliest reaction consists of a superficial decalcification of the enamel of the labial surface of the tooth which is exposed the most. Mastication and tooth brushing wear off the partially decalcified areas and produce flat smooth surfaces. The degree of erosion increases with the length of period of employment. The eroded surface is smooth and polished and never pitted. When the enamel has been destroyed, the dentine is attacked and there is brown or black discoloration of the affected teeth but they retain their polish. While the erosion is taking place the pulp chamber shrinks and the condition is painless except in rare cases where the erosion is so rapid that bacterial invasion of the pulp cavity occurs causing abscess formation. Barsotti *et al.*¹⁵ reported that 19.2 per cent of workers exposed to tartaric acid showed erosion of the incisive and canine teeth. Malcolm and Paul¹⁶ in a study of workers in the storage battery industry reported that workers exposed to acid mist were found to have erosion of the incisor teeth. Gamble¹⁷ in a

study of acid battery workers found that the ratio of observed to expected prevalence of teeth etching and erosion was about four times greater in the high acid-exposure group. The earliest case of etching occurred after exposure for 4 months to an estimated average exposure of 0.23 mg sulphuric acid/m³.

Physical Factors

Occupational injuries may give rise to concussion, loosening or fracture of teeth.

Modifications of the teeth by abrasion occur among shoe makers, upholsterers, glass blowers, dress designers, dress makers and seamstresses. They result from holding nails, tacks, needles, glass tubes and thread reinforced by metals between their teeth. The cobbler holds a ready supply of nails - 30 or so - in his mouth and serves them out from his teeth, and the upholsterer and sofa maker does the same with tacks. Nurses using hairgrips in the same manner sometimes develop changes in their teeth.

Musicians, especially the wind instrument players, develop dental problems. These are mainly the problems of 'embouchure'. The way in which the lips and mouth are applied in the blowing of a wind instrument is known as 'embouchure'. The presence of dental defects can affect the playing of the instruments. The dental problems among wind instrument players have been studied¹⁸⁻²².

Teeth of people who have received harmful doses of X-ray radiations like X-ray technicians, radiographers, research workers and watch dial painters (who lick their brushes) are sometimes affected. Way back in 1925 Hoffman²³ reported four cases in which necrosis of the teeth and jawbones had occurred after the practice of pointing the paint brush with radium on it. The damage by radiation may not appear for several years. The gingivae become inflamed, ulcerated and painful and a foul breath may be present. This may be followed by gingival recession, periodontitis and damage to alveolar bone. The teeth become loose and show resorption of the root. In the later stages, osteomyelitis, osteonecrosis and osteosclerosis of the jaw accompanied by loss of teeth and the formation of sequestra occur. The most common manifestation of radiation injury is a typical destruction of tooth substance resembling dental caries at the cemento-enamel junction and sometimes called 'radiation caries'. Teeth often seem brittle, and pieces of the enamel may fracture away from the tooth. Recent experiences with radiotherapy of malignant diseases²⁴⁻²⁶ have shown that excessive dosage of radiation has severe adverse effects on the teeth.

Increased atmospheric pressure may produce bleeding from gingivae among people working in compressed air chambers. The same complaint may be noticed among aviators due to decreased atmospheric pressure. During the Second World War dental pain was observed in some of the personnel of aircrews flying at high altitude or entering the low pressure chamber. The cause of the pain has been attributed to air embolism being present in the dental pulp. Pain is particularly liable to occur if there is already an inflammatory condition of the pulp.

Effect of Adverse Environmental Factors on Rat Incisors

Comparison between the histology and chemical composition of the incisors of rats acclimatized for 18-24 weeks to cold, neutral or hot atmospheres, at various

parametric pressures showed interesting results. Cold by itself induced negligible histological changes, but altitude (750 or 380 mmHg) produced changes in the mesenchyma of the teeth. These were made severe by superimposed cold (3°C), but superimposed heat (36°C) counteracted some of these effects. The latter group, however, had ectodermal changes. Chemical studies revealed significantly reduced concentrations of calcium, phosphate and magnesium in the teeth of the altitude- and heat-exposed rats. The teeth of rats are continuously growing and this process is similar to the unerupted human tooth formation, and therefore the effects observed in the rats in this experiment may presumably be seen among children if they are exposed to the same conditions.

Because of physiological strains in certain occupations people may develop bruxism or bruxomania, i.e. the habit of constantly grinding their teeth. Athletes engaged in physical activities often develop this habit. The exact reason for this is unknown. Occupations in which the work has to be near precise such as that of the watch maker are likely to cause bruxism. When the habit is firmly established severe searing or attrition of the teeth may occur.

Importance of oral hygiene

Neglect of oral hygiene predisposes the teeth to the development of occupational dental diseases and aggravation of the disease once it occurs. The presence of the aetiological agent alone is not enough to cause dental diseases. The general and oral health of the patient are equally important.

The scope of this paper does not include a consideration of the treatment of various occupational dental disorders. However, there is no denying that prevention of their occurrence is better than a treatment once they occur. Prevention can be effected by proper working conditions and observation of strict oral hygiene. Since oral hygiene is a matter of habit it should be inculcated in early childhood. So that a person is well guarded against any occupational hazard in the course of his employment. Moreover, the training for a particular occupation should include attention to the general health of the worker and particularly to those parts of the body which are exposed to dental occupational hazards. Adequate provision for industrial health should aim at prevention, if possible, or an early recognition and treatment of dental occupational diseases. L'Epee²⁷ has stressed the importance of oral and dental examination as part of the occupational health service.

More studies of occupational diseases of teeth should be conducted in order to check or confirm previous reports and to discover possible manifestations arising among workers in new industries. It is essential for all concerned to have an epidemiological knowledge of the state of oral health of the workers, especially if there are conditions in the industry likely to cause dental disorders²⁸.

REFERENCES

- Peterson PE, Henmar P. Oral conditions among workers in the Danish granite industry. *Scand J Work, Environ Health* 1988; 14: 328.
- Enbom L, Magnusson T, Wall G. Occlusal wear in miners. *Swed Dent J* 1986; 10: 165.
- Gelbier S. Dental health and the chocolate factory. *Occas News Letter, Dental Historian* 1986; 12: 17.
- Gomes ER. Incidence of chromium induced lesions among electroplating workers in Brazil. *Indust Med* 1972; 41: 21.
- Grisolle A. Recherches sur quelquesuns des accidents cerebraux produits par les preparations saturnines, Paris, 1836. Quoted in: Hunter D, ed. *The diseases of occupations*, 4th ed., Aylesbury: Hazell Watson & Viney Ltd., 1969.
- Burton H. *Lancet* 1840; 1: 661. Quoted in Hunter D, ed. *The diseases of occupations* 4th ed., Aylesbury: Hazell Watson & Viney Ltd., 1969.
- Kussmaul A. Untersuchungen uber dem constitutionellen Mercurialismus, Wurzburg; 1861. Quoted in: Hunter D, ed. *The diseases of occupations* 4th ed., Aylesbury: Hazell Watson & Viney Ltd., 1969.
- Vigliani EC, Baldi G, Zurlo N. Chronic mercurialism in the felt hat industry. *Med Lav* 1953; 44: 161.
- Gelbier S, Ingram J. Possible foetotoxic effects of mercury vapour: a case report. *Public Health* 1989; 103: 35.
- Lecovic J, Arnost L. Occupational skeletal fluorosis. *Fluoride Quarterly Reports* 1969; 2: 120.
- Davis HC. George Cunningham; the man and his message. *Br Dent J*, 1969; 127: 527.
- Ward EF. Phosphorus necrosis in the manufacture of fireworks and in the preparation of phosphorus. *Bulletin of the U.S. Bureau of Labor Statistics* 1926; 405: 1.
- Hughes IPW, Baron R, Buckland DH et al. Phosphorus necrosis of the jaw - A present day study with clinical and biochemical study. *Br J Ind Med* 1962; 19: 83.
- Frost DV. Arsenicals in biology - Retrospect and prospect. *Federation Proceedings* 1967; 26: 194.
- Barsotti M, Sassi C, Ghetti G. Health hazards in a tartaric acid factory. *Medicine Del Lavoro*, 1954; 45: 239.
- Malcolm D, Paul E. Erosion of teeth due to sulphuric acid in the battery industry. *Br J Indust Med* 1961; 18: 63.
- Gamble J, Jones W, Hancock J, Meckstroth RL. Epidemiological - environmental study of lead acid battery workers. III. Chronic effects of sulfuric acid on the respiratory system and teeth. *Environ Res* 1984; 35: 30.
- Porter MM. Problems of embouchure comfort: A matter for dental concern. *Scientific and Educational Bulletin of International College of Dentists*, Berkeley, California, U.S.A. 1971; 1.
- Porter MM. The embouchure and dental hazards of wind instrumentalists. *Proc R Soc Med* 1973; 66: 1075.
- Corcoran DF. Dental problems in musicians. *Journal of Irish Dental Association* 1985; 31: 4.
- Farkas P. Medical problems of wind players: a musician's perspective. *Cleve Clin Q* 1986; 53: 33.
- Fine L. Dental problems in the wind instrumentalists. *Cleve Clin Q* 1986; 53: 3.
- Hoffman FL. Radium (Mesothorium) necrosis. *JAMA* 1925; 13: 961.
- Ansell G. *Radiology in clinical toxicology*. Published by London: Butterworth & Co. Ltd., 1974, 146.
- Dury DC, Robert MW, Miser JS, Folio J. Dental root agenesis secondary to irradiation therapy in a case of rhabdomyosarcoma of middle ear. *Oral Surg Oral Med Oral Pathol* 1984; 57: 595.
- Maguire A, Murray JJ, Craft AW, Kernahan J, Welbury RR. Radiological features of the long-term effects from treatment of malignant disease in childhood. *Br Dental J* 1987; 162: 99.
- L'Epee P. The value of oral and dental examinations as part of the occupational medicine service. *Archives Des Maladies Professionnelles* 1969; 30: 428.
- Lesquoy H. Diseases of the teeth of occupational origin. Faculte de medecine, Université de Strasbourg, Strasbourg, France, 1983; 82.

Maladies dentaires d'origine professionnelle

Bibliographie

- * GUPTA B.N. "Occupational Diseases of Teeth", *Journal of the Society of Occupational Medicine*, vol. 40, no. 4, pp. 149-152, (1990).

* Article joint

Risques
chimiques

10 - RISQUES CHIMIQUES

10.1 - Asthme des empaqueteurs de viandes

Le chlorure de polyvinyle, genre de papier cellophane, peut servir à l'empaquetage des viandes. Comme ce plastique transparent est coupé au moyen d'un fil à chaud, les fumées qui s'en dégagent ont déjà causé de l'asthme en particulier chez les empaqueteurs de viandes. Présentement, c'est surtout le polyéthylène qui est employé et on ne rapporte pas de taux élevé d'asthme à l'exposition de ces produits de pyrolyse.

10.2 - Bioxyde de carbone

L'usage de glace sèche pour obtenir une congélation rapide du poulet, du poisson et des viandes a l'avantage d'être rapide et bien utile pour l'industrie du "fast food". Par contre, ce procédé génère des quantités très élevées de CO₂ pouvant facilement passer de 5000 ppm à 50,000 ppm. L'information des travailleurs est essentielle parce que le CO₂ diffuse très rapidement dans les tissus humains et que les centres respiratoires et le système nerveux central répondent rapidement à ce stimulus chimique. Les risques à la santé varient selon la dose. La prévention s'obtient par de la ventilation adéquate ou par l'utilisation de substituts comme l'azote liquide bien que ce dernier comporte des risques à la santé.

Risques chimiques

Bibliographie

- * JACOBS, J.D., SMITH, M.S., "Exposures to Carbon Dioxide in the Poultry Processing Industry", *Am. Ind. Hyg. Assoc. J.*, vol. 49, no. 12, pp. 624-629, (1991).
- * LABROSSE, S., "Dioxyde de carbone : vigilance chez Molson", *Journal de Montréal*, p. 18, (13 août 1991).

* Articles joints

Exposures to Carbon Dioxide in the Poultry Processing Industry

DAVID E. JACOBS and MICHAEL S. SMITH

Georgia Tech Research Institute, Economic Development Laboratory, Environmental, Health, and Safety Division, Atlanta, GA 30332

Use of dry ice has increased dramatically in poultry processing plants because of changes in the fast food industry. Concentrations of carbon dioxide in four such plants were measured and were found to exceed the Immediately Dangerous to Life and Health Level (50 000 ppm) inside holding coolers where ventilation is poor. In other areas, where dry ice is delivered to poultry packages, time-weighted average exposures can exceed the threshold limit value of 5000 ppm by substantial margins, even if local exhaust ventilation systems are present. Reports of adverse health effects from carbon dioxide exposure and various control measures are reviewed. Recommendations regarding sampling and analytical techniques also are presented. Operators of poultry plants where dry ice is used need to recognize the occupational hazards of exposure to carbon dioxide.

Introduction

The growing demand for chicken products in the fast food industry has resulted in an increased use of dry ice (solid carbon dioxide) in many poultry processing plants. Contrary to the conventional wisdom, dry ice is not a harmless substance. The traditional method of using water ice is inefficient because of the longer time required to achieve a deep freeze. This results in some product loss caused by spoilage that could be prevented by use of more rapid freezing techniques. Use of water ice also poses a significant problem in disposal of the liquid water inside the package upon its arrival at the retail outlet, which typically has small storage areas and a need to maintain sanitary cooking and serving areas.

The poultry industry has responded to this demand by including dry ice in poultry packaging. A more rapid freeze is achieved, and there is no cleanup of water required at the retail outlet. Unfortunately, the poultry plants examined here failed to keep occupational exposures to carbon dioxide within acceptable limits.

The toxicity of carbon dioxide is fairly well established. A report of the hazards associated with dry ice refrigeration in the food processing industry appeared as early as 1958, when two instances of near-collapse of aircrew members were described. The airplanes were transporting frozen foods with 12 000 and 7400 pounds of dry ice, respectively. The ability of carbon dioxide to produce adverse health effects rapidly was noted, although concentrations of the gas were not reported.⁽¹⁾

More recently, the National Institute for Occupational Safety and Health (NIOSH) investigated a frozen seafood and meat plant which processes and packages products for fast food distributors. Interviews with employees revealed episodes of headache, eye irritation, dizzy spells, lightheadedness, and shortness of breath. The latter symptom was most prevalent among smokers.⁽²⁾

Carbon dioxide poisoning also has been reported in other work settings, including farm silos,⁽³⁾ fermentation tanks,⁽⁴⁾ wells,^(5,6) shipping,⁽⁷⁻⁹⁾ mining,^(10,11) and fire fighting.^(8,12,13)

Many of these reports suggest that the death or injuries sustained were caused by the toxicity of carbon dioxide and were not caused by oxygen deprivation alone. The Immediately Dangerous to Life and Health (IDLH) level for carbon dioxide is 5% (50 000 ppm). Even at this level, displacement of oxygen by CO₂ is not likely to be significant, since 5% of 20% (the concentration of oxygen in air) is only 1%. Thus, the decline in oxygen concentration by carbon dioxide at the IDLH level should be no more than 1%.

Carbon dioxide has been classified as both a stimulant and depressant of the central nervous system, an asphyxiant, and a potent respiratory stimulant. Rapid breathing, increased heart rate, headache, sweating, shortness of breath, dizziness, mental depression, visual disturbances, shaking, convulsions, unconsciousness, and death can be caused by inhalation of various concentrations of carbon dioxide.⁽¹⁴⁾ The gas can be weakly narcotic at 30 000 ppm, causing reduced hearing and increased blood pressure and pulse.⁽¹⁵⁾ Intoxication can be produced by a 30 min exposure to 50 000 ppm, while exposure to 70 000–100 000 ppm can produce unconsciousness within a few minutes.⁽¹⁶⁾ Because of the extreme sensitivity of various chemoreceptors to CO₂, its high solubility in tissue fluids (20 times that of oxygen), and the permeability of the blood-brain barrier to CO₂, the respiratory and central nervous system responses are immediate.⁽¹⁷⁾

Exposures to carbon dioxide have been shown to cause changes in the body's electrolyte levels and to cause acidosis.⁽¹⁷⁾ Animal studies have indicated that carbon dioxide can affect the reproductive system—causing structural alterations in sperm cells, degeneration of testicular tissue, and congenital spinal malformations—although extrapolation of these findings to humans is problematic at best.⁽¹⁷⁾

The results of surveys of several poultry processing plants indicated occupational exposures to carbon dioxide were well above established limits. The Occupational Safety and Health Administration (OSHA) Permissible Exposure Limit (PEL) and the 1987–88 Threshold Limit Value (TLV®) are both 5000 ppm (8-hr time-weighted average [TWA]). In one

of the plants. concentrations between 50 000 ppm and 90 000 ppm were found, which is above the IDLH level. In a second plant studied here, over 30 employees were reportedly admitted to a hospital after episodes of hyperventilation and dizziness. In a third plant, a worker experienced several episodes of stomach upset and vomiting, also requiring hospitalization.

Experimental Materials and Methods

Exposures to carbon dioxide initially were determined at each of the plants by using short-term, GasTech® Detector tubes (Sensidyne, Largo, Fla.). In one location the results from the GasTech tubes were compared with another brand of detector tubes used by plant supervisory personnel and were found to produce comparable readings. In another location, however, a third brand used by the plant safety manager produced a gradual color change over the entire length of the tube, making an accurate reading difficult. Outdated or inadequate detector tubes were found in three of the four plants studied here. The GasTech tubes used for this study were refrigerated prior to the day of the survey and were used well before the expiration date had passed.

In collecting the samples, care was taken not to include exhaled air while sampling inside workers' breathing zones. Since the partial pressure of carbon dioxide in exhaled breath is normally about 45 mmHg, this contribution to measured exposures is potentially high, as shown by the following calculation:

$$\frac{45 \text{ mmHg}}{760 \text{ mmHg}} = 5.9\% = 59\,000 \text{ ppm}$$

Detector tube measurements of CO₂ taken in an office, however, indicated that background levels were quite low and suggested that exhaled breath is not a significant confounding factor. Measurements were taken near the top of the shoulder, which is where breathing zone samples were taken in the poultry plants. All detector tube samples were taken with the arm fully extended.

The short-term tubes were used to help determine where TWA samples should be taken. Draeger long-term detector tubes (National Draeger, Inc., Pittsburgh, Pa.), which produce a color change from light orange to pale yellow upon exposure to CO₂, were used in one location in an effort to determine the TWA exposure. These tubes were found to be difficult to read accurately because of the difficulty in discriminating between these two colors. Draeger representatives have indicated that others also have reported this problem.⁽¹⁸⁾

A MIRAN® 1A Gas Analyzer (Foxboro Company, South Norwalk, Conn.) also was used in one location in an attempt to measure more accurately the concentration of carbon dioxide. Since most of the workplaces with the highest exposures were inside freezers or holding coolers with temperatures below 4°C, condensation of water vapor inside the instrument chamber was a problem. Even after an hour of continuous operation, the mirrors inside the MIRAN failed to clear. Calibration also proved to be difficult since nitrogen had to

be used to zero the instrument because of the presence of CO₂ in ambient air.

An 8-hr TWA was determined using a bag sampling procedure and gas chromatography (NIOSH Analytical Method 5249). Samples were collected in Tedlar® bags equipped with a Teflon® septum at a nominal flow rate of 20 cc/min. The concentration in the bag was determined in three ways. First, short-term detector tubes were used to measure the concentration of CO₂ inside the bag. To prevent dilution of the analyte, the hose leading to the bag was short and was flushed with the sampled air before the detector tube was attached. The detector tube pump was tested for leaks and calibrated using a bubble/buret method to ensure a nominal sample volume of 100 mL. Second, an aliquot from the bag was transferred to an MDA Vacu-Sampler® (MDA Scientific, Inc., Lincolnshire, Ill.) This step was considered necessary because of previous experience with bag breakage during shipment to the laboratory. Finally, the bags themselves were shipped and analyzed. Upon return, the bags were checked for leaks.

The Vacu-Sampler is an aerosol-type can which has been completely evacuated and then backfilled with nitrogen to a partial vacuum. When activated, 123.3 cc of gas is admitted into the can. The analytical laboratory involved in this study reported that they commonly received containers which had not been completely filled because of the slow-acting valve used on the cans. The valve must be activated for a full 10 sec. Tubing from the bag to the can was kept short and was purged with the gas in the bag before collection.

In general, the direct analysis of the bags in the laboratory gave the lowest results, perhaps because of leakage from the bags during shipment. Laboratory analysis of the Vacu-Sampler cans gave the highest results. On-site analysis of bag air using short-term detector tubes gave results slightly less than the Vacu-Sampler cans. Triple-layered bags were used in Plants 1 and 3, while five-layered bags were used in Plant 4. The latter appeared to be more durable, while three of the triple-layered bags clearly leaked. No bag sampling was performed in Plant 2.

Acceptable TWA air sampling results can be obtained by using five-layered bags followed by on-site detector tube analysis. Sampling lines should be kept as short as possible and should be thoroughly purged prior to analysis. When worn by workers, the bags should be housed in backpacks to prevent tearing. Periodic surveillance is required to ensure that sampling lines do not interfere with bag inflation. It is recommended that these results be confirmed by laboratory analysis of Vacu-Sampler cans containing aliquots of the bag air. Shipment of bags may result in leakage.

Results

The results of initial short-term detector tube sampling in four poultry plants are presented in Table 1. These results suggest that the highest concentrations of CO₂ typically appear inside the holding cooler and that concentrations can exceed or approach the IDLH level of 50 000 ppm. In Plant 1, workers spent nearly the entire shift working on a palletiz-

TABLE I
Initial Short-Term Detector Tube Sampling at Four
Poultry Processing Plants

Plant	Area	Number of Samples	Concentration (ppm)	
			Range	Average
	Breathing zone inside freezer	9	8000-29 000	18 000
	Loading dock	2	5000- 6500	5750
	Dry ice delivery to poultry packages	3	8000-11 000	9000
2	Holding cooler and palletizing area	3	12 000	12 000
	Loading dock	2	12 000-13 000	12 500
	Dry ice delivery to poultry packages	6	5000- 8000	6400
3	Holding cooler	5	23 000-60 000	33 000
	Dry ice delivery to poultry packages (local exhaust present)	6	2700- 5000	3700
4	Holding cooler	3	5000-25 000	18 000
	Palletizing area	2	11 000-30 000	21 000
	Dry ice delivery to poultry packages	4	8000-22 000	12 000

ing operation inside the holding cooler. In Plant 3, on the other hand, entry to the cooler was confined to forklift truck drivers, whose time inside the cooler was brief but frequent. Ventilation in these areas is often quite poor since incursion of outside fresh air is minimized to maintain proper refrigeration. Another survey of a laboratory⁽¹⁹⁾ found levels of 10 000-30 000 ppm in a clean room where air was continuously recirculated through high efficiency particulate arrester (HEPA) filters. Here dry ice was used to achieve quick freezing of pharmaceutical preparations.

The plant safety manager in Plant 3 also collected daily detector tube samples over a 2-month period. Here the range of concentrations inside the cooler was 11 500-96 000 ppm, with the average being 34 000 ppm.

The rate of generation of carbon dioxide gas from dry ice in these work settings is dependent upon a number of variables, including the quantity of dry ice present, the temperature, degree of outdoor air infiltration, size of room, and length of time the dry ice has been present. In holding coolers this latter variable is often quite difficult to quantify since holding time is dependent upon arrival of trucks and variable production schedules. An examination of Table I shows that exposures can be highly variable.

Table II shows the results of bag sampling to determine 8-hr time-weighted average exposures in Plants 1, 3, and 4. All workers monitored had CO₂ exposures above 5000 ppm. Laboratory analysis of aliquots of bag air shipped in Vacu-Sampler cans gave consistently higher results than the other two methods. On-site analysis using short-term detec-

tor tubes yielded slightly lower results, possibly because of failure to identify the exact location of the end of the stain. Laboratory analysis of the bags gave the lowest results, possibly because of bag leakage during shipment.

Discussion

The results presented above indicate that both time-weighted average exposures and short-term exposures can exceed applicable exposure limits. In particular, short-term exposures can exceed IDLH levels. Therefore, poultry processing plants which are using dry ice must develop strategies to control worker exposure; the popular belief that carbon dioxide is "nontoxic" should be dismissed through educational efforts.

Several control alternatives can be considered. Substitution of other methods of quick freezing offer perhaps the best method of controlling the hazard since no carbon dioxide is present with these methods. Some poultry plants have developed freeze tunnels (commonly known as "blast tunnels") which use low-temperature air. The poultry products pass through the tunnel on a conveyor line and then are packaged in insulated, reusable containers. This method requires more rigorous control of temperature inside holding coolers and trucks since no refrigerant is present inside the poultry package itself.

Some versions of blast tunnels use nitrogen instead of air. This alternative still presents some potential hazards since nitrogen can displace oxygen if the nitrogen leaks out of the system in sufficient quantities. Some blast tunnels continue to use carbon dioxide as a refrigerant. Nevertheless, such tunnels represent a more enclosed process and make required exhaust ventilation rates easier to calculate. It should be noted, however, that these tunnels typically require a large amount of plant floor space, sometimes prohibiting their installation in older, smaller plants. Spiral tunnels, which occupy less space, are now available.

Local exhaust ventilation can be used to exhaust carbon dioxide emitted from the machines which deliver the dry ice (which actually is applied in a pressurized, liquid form) to the poultry package. Proper design of the CO₂ delivery system minimizes the amount of CO₂ gas that escapes during application. Poor design results in excessive gas at the point of delivery and will put extra load on the local exhaust ventilation system. Determination of the adequacy of the exhaust ventilation rate often can be determined visually since CO₂ gas appears as smoke. The local exhaust ventilation systems seen in the four plants in this study all had insufficient hood designs and/or ventilation rates which failed to capture the CO₂ generated during package charging. Some local exhaust systems were supplemented with a floor sweep exhaust system designed to remove the heavier-than-air gas that was not captured by the local exhaust system.

These local exhaust ventilation systems typically moved about 2000 cfm (cubic feet per minute). An application engineer employed by a carbon dioxide supplier⁽²⁰⁾ supplied the following rationale for this figure: for illustrative purposes, assume that 500 cfm of CO₂ vapor is generated. Using a safety

dilution factor of 4, and assuming a static pressure drop of 1 in., a 12 in. centrifugal fan operating at 2245 rpm with a 1 horsepower motor should be adequate, since about 2000 cfm would be produced (i.e., $500 \times 4 = 2000$). Thus, given these calculations and the results presented here, it seems likely that better enclosures (possibly producing a static pressure drop greater than 1 in.) and/or faster or larger fans are required.

Local exhaust ventilation systems obviously are not appropriate for controlling exposures inside the holding coolers, where concentrations are the greatest.

Application of normal room dilution ventilation calculations also are difficult since the generation rate of CO_2 gas is highly variable. For Plant 1 the rate of generation was

calculated as follows. Packages containing dry ice gradually were accumulated inside the cooler and then loaded onto trucks twice per shift. If the peak concentration of 30 000 ppm (30 000 $\mu\text{L/L}$) is reached twice per day, and if the temperature is held at 1°C (35°F), then

$$\frac{30\,000 \times 10^{-6} \text{ L/L} \times 44 \text{ g/mole} \times 1 \text{ mole}}{22.55 \text{ L}} = 0.059 \text{ g/L}$$

If the volume of the freezer is 645 000 L, then

$$645\,000 \text{ L} \times 0.059 \text{ g/L} = 38\,000 \text{ g}$$

In short, 38 000 g of CO_2 is generated twice a day

$$\frac{38\,000 \text{ g}}{4 \text{ hr}} = 9500 \text{ g/hr}$$

TABLE II
Comparison of Time-Weighted Average Breathing Zone Samples Using Bag Sampling, Vacu-Sampling® Cans, and Short-Term Detector Tubes^A

Plant	Location	TWA Bag Concentration Measured with Detector Tube on Site (ppm)	TWA Bag Concentration Measured Using Vacu-Sampler and Gas Chromatography in Laboratory (ppm)	TWA Bag Concentration Measured Directly Using Gas Chromatography in Laboratory (ppm)
1	Holding Cooler Worker	4900	5800	3700
	Palletizing Line (Outside holding cooler)	4500	5200	3300
	Dry Ice Packaging Worker 1	4500	6300	3500
	Dry Ice Packaging Worker 2	12 700	13 000	800 ^B
3	Holding Cooler Worker	5600	6400	1900 ^B
	Dry Ice Packaging Worker 1	5900	6600	500 ^B
	Dry Ice Packaging Worker 2	9700	11 500	8000
	Dry Ice Packaging Worker 3	6800	7800	4600
4	Dry Ice Packaging Worker 1	9700	10 800	10 300
	Dry Ice Packaging Worker 2	14 000	15 100	12 800
	Dry Ice Packaging Worker 3	20 000	21 800	25 000
	Holding Cooler Worker 1 (palletizing operation)	9600	10 400	9600
	Holding Cooler Worker 2 (palletizing operation)	14 000	15 300	14 300

^ASampling times were approximately 300 min

^BBags clearly leaked during shipment to laboratory

since the density of carbon dioxide is 1.98 g/L,

$$\frac{9500 \text{ g/hr}}{1.98 \text{ g/L} \times 60 \text{ min/hr}} = 80 \text{ L of CO}_2 \text{ generated per minute}$$

Since carbon dioxide is present in fresh air, the required dilution air volume can be calculated using the following formula:

$$Q_s = \frac{G + (C_o - C_i)Q_e}{C_i}$$

where Q_s = cubic feet per minute (cfm) of supply air needed,
 Q_e = cfm of exhaust air,
 G = rate of generation of contaminate (L/min),
 C_o = concentration of carbon dioxide in outside air (ppm), and
 C_i = target concentration of carbon dioxide inside freezer (ppm).

If one assumes that $Q_e = Q_s$, then

$$Q_s = Q_e = \frac{80 \text{ L/min} + (300 \text{ ppm CO}_2 \text{ in fresh air} - 1000 \text{ ppm})Q_e}{1000 \text{ ppm}}$$

$$Q_e = 47\,000 \text{ L/min} = 1700 \text{ cfm}$$

This calculation assumes a safety factor of 5, since the target concentration is one fifth of the PEL (i.e., 1000 ppm). Conceivably, a lower safety factor could be used because of the relatively low toxicity of carbon dioxide.

An exhaust airflow rate of this magnitude would require a considerable increase in refrigeration capability, since the incoming fresh air would need to be cooled for most of the year. One way of recovering the cost of exhausting contaminated refrigerated air is through the use of an air-to-air heat exchanger. Figure 1 shows a schematic of the system proposed for Plant I.

On a day when the outside air is 35°C (93°F) and the relative humidity is approximately 47%, over 165 000 Btu/hr of heat can be transferred out of the incoming fresh air stream using a properly sized air-to-air heat exchanger. The temperature of the incoming air would be reduced to 13°C (55°F), requiring an additional 138 000 Btu/hr to be removed by the evaporator coil if the air admitted to the cooler is to reach -2°C (28°F). If the heat exchanger were not part of the system, almost 300 000 Btu/hr would have to be removed by the coil. Therefore, the heat exchanger is providing about 55% of the required cooling capacity.

The heat exchanger would need to be fitted with a drain so that condensed vapor is easily removed and does not collect or puddle, thus blocking the heat transfer surfaces. Condensation is desirable in this application since the water vapor in the outside air gives off heat when condensing, which is transferred to the colder exhaust airstream. This results in a higher latent heat transfer rate. Of course, this condensing could cause icing of the downstream evaporator coil. Defrosting of the coil, therefore, is important in ensuring continuous operation.

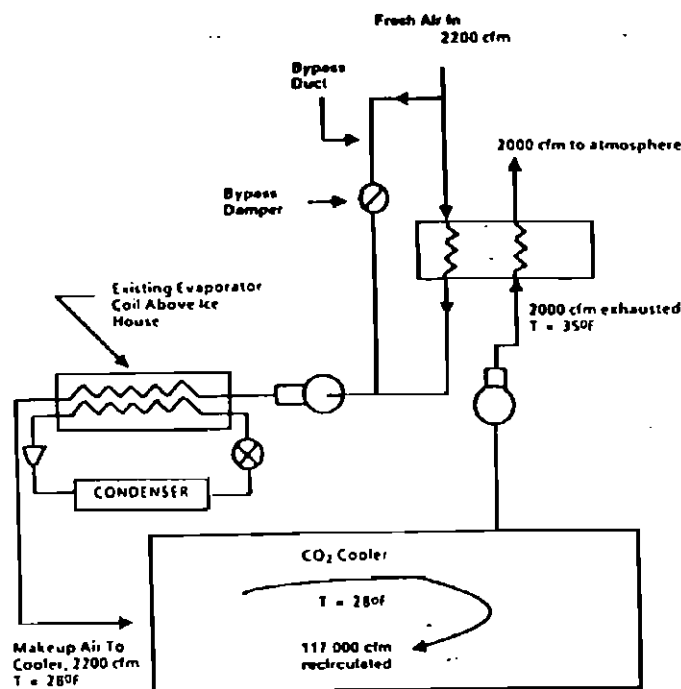


Figure 1—Holding cooler ventilation system

Based on the yearly climate conditions for the location of the plant, the estimated savings are approximately \$8000 per year because of reduced consumption of electrical power. At this rate the cost of the necessary exchanger, the associated ductwork, the dilution ventilation system, and the refrigeration coil modifications could be recovered in less than one year.

Several factors were not included in this economic analysis. The efficiency of the refrigeration system compressor in converting electric power into cooling was neglected. This will underestimate the actual savings, since an efficiency of 100% was assumed. On the other hand, the cost of operating the exhaust stream fan and the fresh air fan was neglected, which will overestimate the savings. Actual savings also will vary with outside weather conditions and system operating time.

Administrative controls also can be effective for this application. In Plant I, workers involved in a palletizing operation inside the holding cooler were relocated. By transferring this operation into the larger plant area (which is equipped with a floor sweep exhaust system), exposures were reduced considerably. Short-term detector tube sampling indicated that exposures declined from a range of 8000-29 000 ppm to 3000-6000 ppm. The TWA measured at this location (after the workers had been transferred out of the cooler) was 4500 ppm. Alarm systems which warn of high carbon dioxide concentrations inside the holding cooler are recommended since short periods of high exposure appear to be inevitable.

Conclusion

Poultry plant operators should be aware of the dangers of occupational exposures to carbon dioxide resulting from use

of dry ice. Hospitalization and death caused by overexposure to carbon dioxide have been reported. The increasing use of dry ice in the poultry industry could increase the level of risk faced by employees. Control of exposures can be achieved through the use of properly engineered local exhaust ventilation for machines which discharge dry ice into poultry packages. For holding coolers, where exposures can be extremely high, dilution ventilation appears to be the only possible control method. An air-to-air heat exchanger can help pay for the cost of such a dilution ventilation system. Short of this, relocation of workers out of holding coolers can reduce exposures considerably. Finally, alternative methods of refrigeration should be considered, including blast tunnels, super-cooled air, and use of liquid nitrogen. These alternatives still possess occupational hazards that need to be evaluated.

Acknowledgment

This study was funded in part by grants from the U.S. Department of Labor and Georgia Tech's Agricultural Research Project. Special thanks to Yvonne Thomas for manuscript preparation are in order.

References

1. Nutall, J.B.: Hazards of Carbon Dioxide. *J. Am. Med. Assoc.* 168 (Dec. 13):1962 (1958).
2. National Institute for Occupational Safety and Health: *NIOSH Technical Assistance Report HETA 85-093* by S.A. Salisbury. Atlanta, Ga.: Department of Health and Human Services, August 28, 1985.
3. Troisl, F.M.: Delayed Death Caused by Gassing in a Silo Containing Green Forage. *Br. J. Ind. Med.* 14:58 (1957).
4. Pedersen, M.B. and J. Simonsen: Accidental Death in Fermentation Tanks: Report of Two Cases. *Med. Sci. Law.* 22:283-284 (1982).
5. Sevel, D. and A. Freeman: Cerebro-Retinal Degeneration due to Carbon Dioxide Poisoning. *Br. J. Ophthalmol.* 51:475-482 (1967).
6. Fedorowicz, A. and W. Badach-Rogowski: Carbon Dioxide Poisoning. *Polski Tygodnik Lekarski.* 24:21-22 (1969). [Polish].

7. Williams, H.I.: Carbon Dioxide Poisoning. *Br. Med. J.* Oct. 25:1012-1014 (1958).
8. Brighton, P.: A Case of Industrial Carbon Dioxide Poisoning. *Anaesthesia* 31:406-409 (1976).
9. Dalgaard, J.B.: Fatal Poisoning and Other Health Hazards Connected with Industrial Fishing. *Br. J. Ind. Med.* 2:1012-1014 (1958).
10. Tarnawski, S., J. Wolanczyk, J. Lazowska-Jurkalis, K. Szadok, R. Niznikiewicz and W. Pirog: Acute Carbon Dioxide Poisoning in Miners of One of the Coal Mines in Walbrzych. *Med. Pr.* 18:19-194 (1967). [Polish].
11. Duchrow, G.: Analysis of a Case of Mass CO₂ Poisoning from the Standpoint of Mine Safety. *Bergakademie.* 17:208-214 (1965). [German].
12. Fibers, Plastic Fumes Cause Smoke Deaths. *Int. Fire Fighter.* 56:4-5 (1973).
13. Vogelenzang, J.E.: Massive Poisoning with Carbon Dioxide. *Tijdschr. Soc. Geneesk.* 40:249-254 (1962). [Dutch].
14. National Institute for Occupational Safety and Health: *NIOSH/OSHA Occupational Health Guidelines for Chemical Hazards* (DHHS Publication No. 81-123). Cincinnati, Ohio: National Institute for Occupational Safety and Health, 1981.
15. Aero Medical Association: Committee on Aviation Toxicology. Balkiston, NY 1953. Cited in *Documentation of Threshold Limit Values*, 5th ed. Cincinnati, Ohio: American Conference of Governmental Industrial Hygienists, 1986.
16. Flury, F. and F. Zernik: *Schadliche Gase und Dampfe [Poisonous Gases and Fumes]*. Berlin: J. Springer, 1931. Cited in *Documentation of Threshold Limit Values*, 5th ed. Cincinnati, Ohio: American Conference of Governmental Industrial Hygienists, 1986.
17. National Institute for Occupational Safety and Health: *NIOSH Criteria for a Recommended Standard . . . Occupational Exposure to Carbon Dioxide* (HEW Publication No. 76-194). Washington, D.C.: Public Health Service, August 1976. pp. 24, 93, 97-98.
18. Author discussion with Draeger representative, American Industrial Hygiene Conference, Dallas, Texas, 1986. Contact D. Jacobs, Georgia Tech Research Institute, Economic Development Laboratory, Environmental, Health, and Safety Division, Atlanta, Ga. 30332.
19. Jacobs, D.: Industrial Hygiene Survey of Lee Laboratories, Atlanta, Ga., March 1, 1985. [Unpublished Report].
20. Lane, Terence: "Carbon Dioxide Vapor and Exhaust Ventilation Systems." [Private Conversation]. Terence Lane, Liquid Carbonic Company, Carbon Dioxide Division, 1635 Phoenix Blvd., Suite 17, Atlanta, GA 30349.
19 January 1988; Revised 22 June 1988

TV

aisse, chartier
Et associés inc.

MONTRÉAL

LE DEVOIR/PREMIERE 11 10
LE JOURNAL DE MONTRÉAL/FINALE 11 11
LA PRESSE/PREMIERE 11 12
THE GAZETTE/FIRST 11 13

Code 84

Page 18

MARDI 13 AOUT 1991

QUI AU LENDEMAIN / OVERNIGHT CANADA

Dioxyde de carbone: vigilance chez Molson

La Brasserie Molson O'Keefe devra, si ce n'est déjà fait, modifier substantiellement son système de sécurité pour parer à toute évacuation dangereuse de dioxyde de carbone, provenant de la fermentation de la bière, dans ses salles de travail.

Serge Labrosse

C'est en résumé la recommandation qu'a transmise aux autorités concernées, il y a quelques semaines, le coronar Jose-Luis Labarias, de Montréal.

Cette recommandation, qui inclut notamment la mise en place de systèmes d'alarme et de ventilation, est le fruit d'une enquête qu'a menée le coronar Labarias sur les circonstances

malheureuses ayant entraîné le décès d'un employé de Molson-O'Keefe, le 21 décembre dernier: M. Claude Provost.

Monsieur Provost, un opérateur à la salle des machines de la brasserie depuis 23 ans, fut découvert inconscient par ses collègues dans la salle dite «de dioxyde de carbone» de l'usine ouest, située au 485 rue Peel, à Montréal.

* L'enquête menée par la Commission de santé et sécurité au travail a démontré que la Brasserie récupère le dioxyde de carbone afin de le réutiliser sous forme gazeuse, explique le coronar dans son rapport.

Le processus permettant d'emmagasiner le CO2 implique notamment l'utilisation d'un liquéfacteur, que M. Provost s'était précisément rendu activer, lorsque l'accident mortel s'est produit.

Vingt bonnes minutes se sont toutefois écoulées avant que les collègues de travail de la victime, dans une salle adjacente, ne décèlent dans l'air ambiant l'odeur qui leur a fait prendre conscience du drame qui s'était joué...

Ceux-ci se sont immédiatement portés au secours de la victime, mais toutes les manoeuvres de réanimation sont restées vaines et M. Provost a succombé à l'asphyxie.

L'enquête a révélé qu'en cas de surpression (ce qui s'est produit ce jour-là), le dioxyde de carbone est évacué par une soupape de sécurité.

Mais comme il n'y avait pas de détecteur de CO2, le seul indice permettant aux employés d'être informés d'une fuite était celui des «odeurs» émanant du point de fuite...

L'absence de tout autre système d'alarme a été fatal pour la victime.

F 8414
Vol.3
Ex.2