

Use of the specific challenge in the diagnosis of occupational asthma: a 'gold standard' test or a test not used in current practice of occupational asthma?

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Purpose of review

This review, an assessment of the role of inhalational challenge testing in the diagnosis of occupational asthma, focuses on the difficulties associated with making the correct diagnosis of occupational asthma. This report contrasts the apparent discrepancy between the clinical diagnosis and the diagnosis made by inhalational challenge testing, the 'gold standard'. This disparity has been pointed out by a number of authors, yet this approach to making the diagnosis of this illness continues.

Recent findings

Because of the disparity between the clinical mode for diagnosis and using specific challenge testing for diagnosis, awarding compensation to a worker based on the clinical diagnosis of occupational asthma, or using this clinical approach to identify the incidence or prevalence of occupational asthma in a population, is suspect. In the absence of specific inhalational challenge, physicians have attempted to understand changes in flow rates over time through the use of serial peak-flow assessments, a relatively cost-effective way to sort out the diagnosis. Yet, there is an increasing body of knowledge which presents information casting concern on the adequacy of these measurements. In addition, recent data suggest that chest physicians, occupational medicine physicians, and allergists most often make a diagnosis of occupational asthma by usual clinical methodology, which is a routine part of their hospital's pulmonary function laboratory.

Summary

The apparent lack of training in the approach to specific inhalation challenge testing in fellowship programs, the relatively few specialized centers, and the apparent lack of recognition by many physicians who are presented with a patient with suspected occupational asthma means that the use of routine methods to make the clinical diagnosis may often be incorrect, making it unlikely that this approach to the diagnosis of occupational asthma will change in the near future.

Keywords

occupational asthma, inhalational challenge tests

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Abbreviation

RADS reactive airways dysfunction syndrome

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Introduction

An accurate diagnosis of occupational asthma can be made if four prerequisites are met. The diagnosis becomes less firm if fewer criteria are met. These four criteria include (1) the worker has developed asthmatic complaints *de novo*; (2) an objective diagnosis of asthma is made; (3) a temporal relationship exists between workplace exposure and the respiratory complaints; and (4) a specific sensitizing agent in the workplace can be shown to provoke asthma at nonirritant exposure levels [1]. Although such a definition appears to be straightforward, implementing these criteria in attempting to make the diagnosis of occupational asthma can be problematic.

First, the worker must be shown to have asthma, *de novo*. Specifically,

- (1) Not all workers in the workplace have 'true' occupational asthma, that is asthma attributable to a specific sensitizing agent. For example, workers with underlying asthma may develop episodes within the workplace to nonspecific irritants, or to molds or other antigens which may be endemic in the workplace, independent of a specific sensitizing agent. In both instances, the recognition of respiratory symptoms associated with work exposures would result in the same solution – the worker must leave the workplace.
- (2) A proposal has been made to further expand the definition of occupational asthma to go beyond the commonly accepted 'sensitizer-induced asthma' and reactive airways dysfunction syndrome (RADS) to include workers who have preexisting asthma exacerbated by workplace irritant exposures [2]. Although this may be relevant when one addresses the social impact of asthma in the workplace, this is not the traditional definition whereby a specific sensitizing agent unique to the workplace initiates a worker's asthma.

Second, the physician must prove a diagnosis of clinical asthma. In many instances, this is not difficult, however

there are circumstances which are recognized in association with the diagnosis of asthma in the occupational setting which reflect how complex this may be.

- (1) 'Vocal cord dysphonia', a 'psychologic' syndrome which results in vocal cord dysfunction in association with occupational exposures.
- (2) The absence of nonspecific airway hyperresponsiveness in the presence of occupational asthma. Although this is unusual when the worker has active asthma, such instances are well recognized and have been reported by a number of investigators. The absence of 'airway hyperresponsiveness' does not rule out sensitization to an occupational sensitizer.

Third, the worker's asthma must be shown to occur in association with workplace exposures. There are several important caveats with these criteria.

- (1) Regardless of cause, workers who feel bad or complain of respiratory problems at work typically have fewer symptoms and feel better away from work.
- (2) The presentation of occupational asthma is variable. Some who become sensitized develop asthma symptoms immediately upon exposure (hence, the term 'immediate-onset' asthma), while other sensitized workers develop asthma symptoms after several hours in the workplace ('late-onset' asthma). In this latter example, it is much more difficult to relate the episode to a workplace exposure. Of course, some workers may present with both immediate-onset and late-onset asthma.
- (3) The time from the worker's first respiratory symptoms and the identification of the association between asthma and the workplace, and the critical response of removing the worker from the workplace are key. The likelihood of resolution of all chest complaints increases if the time from symptoms to diagnosis is less than 6 months. When the time for diagnosis exceeds this, there is a time-dependent increase in the risk for persistent asthma.
- (4) Occupational asthma, depending on its duration in an individual, can appear to have a straightforward relationship to exposure, or it can be more complex. For example, those who have only recently been sensitized may only have asthma when around the specific sensitizer. When the presence of asthma has become more 'rooted' and sensitization has continued, asthma may persist, independent of exposure to the sensitizing agent. In such cases, nonspecific irritants provoke asthma symptoms. Finally, in the unusual but well described presentation of 'recurrent late asthma', workers who have had episodes of 'late-onset' asthma for a long duration and who continue workplace exposures

may have episodes of asthma at approximately the same time on days when no occupational exposure has occurred.

- (5) Finally, it is not surprising that data from numerous laboratories show that the clinical diagnosis of isocyanate-induced asthma is made more often than it can be proven by objective criteria. The failure to identify asthma caused by a specific sensitizing workplace agent could result in a worker's death due to asthma [3,4]. For this reason, the physician is more likely to err on the side of making the diagnosis.

Fourth, occupational asthma must be related to a specific sensitizing agent present in the workplace.

- (1) The presence of a respiratory sensitizer in the workplace is insufficient to state cause and effect in the diagnosis of occupational asthma. As noted, workers with underlying asthma may develop asthma symptoms within the workplace to non-specific irritants or to antigens which may be a part of the workplace. This occurs independent of a specific sensitizing agent.
- (2) Serologic tests are often very complex, but can be very helpful if the measurement is accurate and reliable [5]. Although there is a reasonable fund of information showing that the use of skin tests or RAST is useful in the diagnosis of occupational asthma caused by large molecular weight agents, the serologic diagnosis of occupational asthma to small molecular weight remains problematic. It is in this group of workers that specific inhalation tests is most relevant. Skin tests to these small molecular weight agents are typically irritating. Although there are reports showing that serum immunologic tests may be relevant in the diagnosis of occupational asthma, the widespread use of such tests is not available and they have not been shown to be reproducible in different laboratories. For this reason, much of the literature regarding the usefulness of specific inhalation challenge testing has addressed asthma attributable to these agents.

It is in the context of the third and fourth diagnostic criteria that the question asked in the title of this manuscript becomes relevant. What is the role of specific challenge testing in the diagnosis of occupational asthma?

Can physicians reliably make an accurate clinical diagnosis of occupational asthma?

In the late 1980s and early 1990s, a series of reports showed the discord between the clinical diagnosis of asthma and occupational asthma proven by specific

inhalation challenge tests. Mapp *et al.* [6] were the first to report the disparity between the clinical diagnosis of isocyanate-induced asthma and the diagnosis of isocyanate-induced asthma by specific challenge testing. Of 165 workers suspected clinically to have isocyanate-induced asthma, only 56% had a positive response to isocyanate challenge. Later, a subgroup of these workers were described in more detail [7]. Moller *et al.* [8] reported challenge testing results on 12 workers with a clinical and occupational history consistent with isocyanate-induced asthma. Only seven responded to specific inhalation challenge. In another series, 63 workers with a physician's diagnosis of isocyanate-induced asthma were referred for isocyanate challenge testing [9]. Thirty-three were proven to have no specific airway responsiveness to subirritant levels of isocyanates, yet 88% of the nonresponders reported work-related respiratory tract complaints and 97% of these same nonresponders noted an improvement in chest complaints when away from the workplace. To make the diagnosis even more difficult, 43% of those who did not respond to isocyanate challenge possessed airway hyperresponsiveness to methacholine, confirming the fact that this test may help with the diagnosis of asthma, in general, but not in the identification of the agent.

In another report [10], 162 workers were evaluated because their referring physician considered that their asthma might be work related. A medical questionnaire included questions about the nature of the symptoms (dyspnea, wheezing, cough, and chest tightness) and the timing (worse at work or after a shift at work or improved during weekends or holidays). An initial clinical assessment was set by the physician on a scale that ranged from highly probable to probable, uncertain, unlikely, or absent. Seventy-two underwent specific inhalation challenges, 29 had serial monitoring of peak expiratory flow rates for periods at work and away from work, and 61 had both. Although all had clinical complaints consistent with occupational asthma, only 75 workers (46%) were shown to have occupational asthma by objective assessment.

Based on these data, it has become clear that the diagnosis of occupational asthma cannot be reliably made by the 'history, physical examination, lung function tests, and methacholine inhalation test', the 'objective strengths' of the pulmonary and occupational physician. Indeed, when specific inhalation challenge testing is performed, approximately half who present with complaints thought to be occupational asthma do not have asthma induced by the specific agent tested.

Why is there such disparity between the clinical diagnosis of occupational asthma and specific inhalation challenge testing? One possibility might be that the

referral population in these reports was not representative of those with occupational asthma. This seems unlikely because, first, challenged workers were referred from different workplaces by different physicians in these three large studies and, second, all studies reported a high prevalence of the same respiratory complaints. A second possibility might be that workers had 'recovered' from occupational asthma and were no longer sensitive to the specific sensitizing agent. In this situation, a negative challenge test might be a false-negative test. Such a report in a worker with isocyanate-induced asthma has been described [11]. This appears to be unlikely on a large scale, however. At least in those with occupational asthma attributable to large molecular weight agents, workers can lose their nonspecific bronchial responsiveness (and explain some who have normal airway responsiveness) while maintaining their specific bronchial hyperresponsiveness to the sensitizing agent even after a substantial time away from the workplace [12,13]. In this population, specific IgE to the specific antigen persists. Finally, it is certainly possible that in some instances specific inhalation testing may be negative but the worker has occupational asthma. In this case, the worker could have been tested with the wrong agent.

There is a considerable amount of data to show that physicians cannot reliably make a clinical diagnosis of occupational asthma, and although this has been most often recognized in small molecular weight agents, there have been recent reports which emphasize this difficulty in addressing asthma attributable to large molecular weight agents [14]. Many workers referred for specific inhalation challenge testing to a workplace agent have asthma, but this illness may not be the result of exposure to a workplace sensitizing agent. Asthma symptoms may well become more pronounced in an atopic individual who is exposed to antigens in the workplace.

Are epidemiologic studies which estimate the prevalence of work-related asthma in a population accurate?

In the past several years, there have been a series of reports attempting to define the prevalence of work-related asthma. These reports can be grouped into three categories: the first attempts to define the prevalence of asthma in a population who have exposure to potentially 'sensitizing' agents and comparing these results to those not exposed; the second is surveillance in a population, that is how many in the population answer positively to questions which allow for the identification of work-related asthma; and the third, assessment of the incidence of occupational asthma among workers who have sought medical help [15]. This requires accurate reporting by physicians, hospitals or worker compensation agencies. A critical factor in determining how much

asthma in adults may be related to occupational exposures depends on the definition used and whether the study is developed to address the question of the work-relatedness of occupational complaints. Overall there are numerous studies, all with a variety of definitions.

A series of reports describing the work-relatedness of asthma in different countries showed that occupational exposure caused or exacerbated asthma in 5–10% [16]. Blanc and Toren [17] reviewed a number of reports which included new onset and reactivation of preexisting asthma as being attributable to workplace exposures. The range of attributable risk was between 2 and 33%, with a median of 9%.

The largest report and most recent report describes the relationship between the workers' upper and lower respiratory health and their employment by industry collected from a representative sample of 40 000 noninstitutionalized individuals from 1988 to 1994 [18•]. Although there were no direct questions to address the proportion of asthma related to workplace exposure (and thus making one concerned regarding the validity of the definition of asthma related to workplace exposure in this report), the investigators assembled the results of several questions to define (1) the prevalence of physician diagnosed work-related asthma, and (2) symptoms of work-related wheezing. In individuals between 20 and 44 years, the prevalence of these entities was 3.8 and 13.1%, respectively. Liss and Tarlo [19], in an editorial addressing this report, pointed out several concerns which are a part of many large epidemiologic surveys, attempting to relate work and health. These concerns include first that the definition of 'exposure' is self reported; second, workers were categorized by the 'longest industry worked in', even though other employment had a potential to induce asthma; third, many workers might have left the workplace due to respiratory complaints and the current workers were not representative of all who began employment (the 'healthy worker effect'); and finally, the questions asked did not allow for the discrimination between sensitizer-induced occupational asthma versus irritant-induced asthma versus work-aggravated asthma, or even unrelated coincidental asthma or other causes of symptoms.

In the most recent *Morbidity and Mortality Weekly Report* [20] summarizing the efforts to understand the incidence of occupational asthma in the US, it is difficult to understand the incidence of this disease. The authors described work-related asthma to include work-aggravated asthma (worsening asthma in those with known asthma) and new-onset asthma. The category of new-onset asthma included RADS and occupational asthma

with or without exposure to a known sensitizer, and with or without objective evidence of the illness. A total of 1101 work-related asthma cases were reported. Nineteen percent were work-aggravated asthma, 12% were RADS and 69% occupational asthma. The data were examined in more detail in two states. Of 562 workers, 19 had medical records which documented lung function which supported a relationship between work and asthma. The validity of the diagnosis in this population is not clear. Of the 562, 13 documented occupational asthma by cross-shift spirometry (perhaps the least effective way to document workplace airway events [21,22]), and six documented this illness with serial peak flow rate measurements. More objective means to document the work-relatedness of asthma were proposed for future studies.

Physicians in the UK have attempted to understand the incidence of occupational lung disease since 1989. A recent report from the Surveillance of Work-Related and Occupational Respiratory Disease program [23] focuses on the experience associated with occupational asthma from 1989 to 1997. During this time, 7387 cases of occupational asthma were reported. Criteria for entry, and therefore the diagnosis of occupational asthma, were intentionally brief and simple. Precise criteria and definitions were not imposed because of the variations that exist in clinical opinion and the availability of evidence for causation among participating physicians. Physicians were asked to identify newly reported cases that they thought were caused by exposure at work. In another report addressing the health of this worker population, it appears that specific criteria for diagnosis are available for some occupational illnesses (such as a pathology report for mesothelioma), but no specific statement regarding diagnostic criteria for asthma associated with the workplace was presented [24].

In the final epidemiologic report cited (although other countries are attempting to identify the incidence of occupational asthma [25]), representatives from South Africa have reported their conclusions for the first 2 years (1996–98) that the nationwide Surveillance of Work-Related and Occupational Respiratory Diseases in South Africa has been in place [26]. Physician reporting is voluntary and information submitted includes the disease, and the industry and the job in which the illness occurred. A more detailed form for each case of occupational asthma collected additional information, including the method of diagnosis and subsequent history of the patient. Two hundred and twenty-five cases of occupational asthma were reported.

In summary, epidemiologic studies which lack specific criteria for the diagnosis of occupational asthma have pluses and minuses. There is extensive information,

cited above, clearly recognizing that the accurate diagnosis of occupational asthma requires objective criteria. Although these reports may be useful in determining trends or identifying clusters in specific industries or among geographically related populations, they are very disappointing in helping us to understand the impact of the workplace on the worker's respiratory health. There are several explanations for this. First, the criteria for the diagnosis of occupational asthma are not consistent among the reports; second, the questions posed may or may not be appropriate to answer the work-relatedness of asthma; third, it appears that in most instances, epidemiologic diagnoses are not validated by specific inhalation challenge testing or serology; fourth, in a number of instances, it is not clear whether the asthma that is reported is induced by a sensitizer or the result of an irritant causing worsening of underlying asthma; and finally, the excessively broad range of attributability of the effect of the workplace in causing or exacerbating respiratory complaints (note Blanc's report citing the range of attributable risk for workplace exposure to be between 2 and 33%) makes it unclear how confident one should be in these reports.

There is a dearth of information relating epidemiology and specific inhalation testing, and I am aware of one report validating the new onset of respiratory symptoms and specific inhalation challenge testing. Workers were serially assessed for the first 2 years of a newly opened workplace engaged in the manufacturing of isocyanates. All who developed respiratory complaints were evaluated with specific inhalation challenge testing. Eleven of 130 were shown to be sensitized, yielding a 5% incidence over a 2-year period, or approximately 2.5% per year [27].

How good are other tests in diagnosing occupational asthma?

There appears to be no clear consensus regarding what is appropriate in the diagnosis of occupational asthma among many US physicians who address worker respiratory health. Ortega *et al.* [28**] reported a questionnaire study of 259 program directors of occupational medicine, pulmonary diseases, and allergy and immunology. Of 123 respondents, 92 reported that they had evaluated workers with suspected occupational asthma in the past year and reported method(s) that they used in making this diagnosis. Thirty-two (37%) diagnosed occupational asthma by history alone, 67 (73%) required spirometry and a consistent history, 61 (66%) were based on history and serial peak flow measurements, and 72 (78%) required a consistent history and measurement of nonspecific bronchial hyperresponsiveness. In only 15 (16%) was specific inhalation challenge testing performed, although in 10 others, workers were referred for specific inhalation testing.

Peak flow monitoring was assessed [29] in 23 workers for at least 2 weeks at work and then away from work and the results were compared with specific inhalation testing. If the three individuals with unsatisfactory peak flow monitoring were excluded, 12 of 20 were proven to have occupational asthma by both peak flow monitoring and positive specific inhalation challenge. No discordance between these two tests was recorded. Liss and Tarlo [30] assessed peak flow records in 78 workers with suspected occupational asthma. Results from 28 (36%) were excluded because of unacceptable measurements. In 50 acceptable tests, the information was unhelpful in 13 (26%). Yet, when an accurate objective interpretation could be performed, there was good sensitivity (93%) and specificity (90%) for occupational asthma. Similar high sensitivity and specificity of peak flow recordings were reported in red cedar workers when peak flow readings and specific challenge results were compared [31]. Thus in workers who can perform and accurately record adequate peak flow readings, this approach can be useful.

Despite this encouraging starting point, investigators have recognized two difficulties with the use of the peak flow meter. The first is guaranteeing accurate measurements and the second is providing an accurate interpretation of the collected information. The data are best if the physician has been able to assess the worker for respiratory symptoms and correlate them with the adequacy of spirometry efforts. Yet, important flaws may exist with this approach. As previously noted, episodes of asthma following exposure to common allergens, exertion, or cold may be associated with the workplace environment or the job itself and result in respiratory symptoms independent of workplace exposure. In addition, the workplace atmosphere may not be controllable. On one day essentially no sensitizing agent exposure could occur, in which case the diagnosis of occupational asthma would be missed, whereas on another day the sensitizing agent exposure might be excessive and cause a decline in lung function and symptoms provoked by an irritant exposure. To complicate matters further, numerous chemicals other than the sensitizing agent may be present in the workplace and act as irritants and precipitate asthma. Therefore, although one may be able to make a diagnosis of occupational asthma, this approach does not identify the toxicant. This is not surprising in the face of information showing that more than 200 agents can induce occupational asthma [32,33]. A qualified industrial hygienist to accurately assess the workplace environment can be of inestimable help.

Importantly, routine peak flow measurements are without a 'hard copy', and the values recorded may not reflect optimal effort or correct values. Quirce *et al.* [34]

emphasized this by attempting to objectively identify occupational asthma in symptomatic workers by measuring peak flow rates in a unit which stored the readings in a small, portable computer which also provided a digital readout, as well by asking workers to keep a diary recording the values. Workers were unaware that the readings were recorded by the monitoring device. Fifty-five percent of the records were accurate in recording the value and timing of the measurements, 23% were inaccurate either in the recorded value or timing, and the rest of the tests were fabricated. Similar results were reported by Malo *et al.* [35]. In both reports, significantly worse compliance was found in workers referred by the Workers' Compensation Bureau. These data complicate the approach to the assessment of the use of the peak flow meter in the assessment of occupational asthma. Hankinson [36] has recently addressed these concerns in detail.

The second problem, difficulty in interpreting serial peak flow rate measurements, has led investigators to develop a computerized assisted diagnostic aid, the Occupation Asthma System (OASYS-2), based on a scoring system developed from visual analysis and validated with standard sets [37]. Additional testing of this program has shown that there is considerable variation in interpretation of serial peak flow rates in the assessment of occupational asthma, not only among the experts, but also between the experts and the computer program, even when the tracings showed a very high probability of occupational effect [38•].

A second objective way of measuring changes in the lung function is to assay bronchial hyperresponsiveness to methacholine or histamine at the start and the end of the work week, and then repeat this measurement after 10–14 days away from work. A significant improvement in histamine or methacholine reactivity away from work supports the diagnosis of occupational asthma. Yet, the sensitivity and specificity of these paired tests relative to isocyanate challenges has not been reported. In red cedar workers, however, the sensitivity and specificity were less than those for peak flow monitoring [31]. A lack of improvement in methacholine response away from work does not exclude occupational asthma, since a significant improvement (a greater than threefold improvement in the concentration causing a 20% decline in forced expiratory volume in 1 s [PC_{20}]) may not occur for up to 45 months, if at all [38]. In addition, as with peak flow rate changes, a significant worsening of nonspecific bronchial hyperresponsiveness into the asthmatic range with exposure to the sensitizing agent may only occur after 10–14 days back at work in a sensitized worker whose asthma had resolved off work [40]. Similarly, normal methacholine responsiveness has been reported even after a definite positive isocyanate challenge [41]. Never-

theless, a normal methacholine or histamine response within 24 h of the worker's usual respiratory symptoms with workplace exposure makes the diagnosis of occupational asthma very unlikely, and correlates well with negative peak flow results [30]. Thus paired methacholine tests can be a useful adjunct to serial peak flow monitoring (when it is valid), but interpretation appears to be limited.

Conclusion

The diagnosis of occupational asthma should be entertained when an exposed worker first reports respiratory symptoms. There are few more difficult challenges in the practice of occupational lung disease medicine than attempting to identify occupational asthma on the basis of a review of a worker's records or by an interview of the worker.

There are a number of pitfalls associated with the diagnosis of occupational asthma [42], some of which are described above. The numerous epidemiologic reports present a greatly varied picture of the impact of the workplace on the worker's respiratory health. In a number of instances, epidemiologic reports of occupational asthma require no case definition – only the physician's diagnosis. At least in the US, physicians use many different ways to make the diagnosis, some with a very low reliability. Testing workers while they remain employed allows them to be carefully and objectively monitored in the same environment where symptoms have occurred. Regrettably, this is not always possible. The two easiest ways to develop objective data which appeared to be very reasonable in the 1980s and 1990s, serial peak flow measurements and paired methacholine tests, have become less attractive and provide less reliable information as investigators have become more knowledgeable about the pitfalls associated with these approaches.

When the above tests are completed, and if serology is not available, there remains an additional objective test, the specific inhalation challenge test in the laboratory. Yet, it is costly and requires a multi-disciplinary approach, which allows this specialized work to be safely performed. Although it is not used as widely as it could be, it clearly is very appropriate when other approaches have not provided a convincing answer to questions about the worker's respiratory health.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

- 1 Banks DE, deShazo RD. Overview of occupational asthma. *Immunol Allergy Practice* 1985; 7:122–130.
- 2 Wagner GR, Wegman DH. Occupational asthma: prevention by definition. *Am J Ind Med* 1998; 33:347–349.

- 3 Fabbri LM, Daniele D, Criscioli S, *et al.* Fatal asthma in a subject sensitized to toluene diisocyanate. *Am Rev Respir Dis* 1988; 137:1494–1498.
 - 4 Liss GM, Tarlo SM, Banks D, *et al.* Preliminary report of mortality among workers compensated for work-related asthma. *Am J Ind Med* 1999; 35:465–471.
 - 5 Guidelines for the diagnosis of occupational asthma. Subcommittee on 'Occupational Allergy' of the European Academy of Allergology and Clinical Immunology. *Clin Exp Allergy* 1992; 22:103–108.
 - 6 Mapp CE, DiGiacomo CR, Zedda L, *et al.* Isocyanate-induced asthma: a review of 165 cases studied in 1983–1985 [abstract]. *J Allergy Clin Immunol* 1986; 77:17.
 - 7 Karol MH, Tollerud DJ, Campbell TP, *et al.* Predictive value of airways hyperresponsiveness and circulating IgE for identifying types of responses to toluene diisocyanate inhalation challenge. *Am J Respir Crit Care Med* 1994; 149:611–615.
 - 8 Moller DR, Brooks SM, McKay RT, *et al.* Chronic asthma due to toluene diisocyanate. *Chest* 1986; 90:494–499.
 - 9 Banks DE, Sastre J, Butcher BT, *et al.* Role of inhalation challenge testing in the diagnosis of isocyanate-induced asthma. *Chest* 1989; 95:414–423.
 - 10 Malo JL, Ghezzo H, l'Archeveque J, *et al.* Is the clinical history a satisfactory means of diagnosing occupational asthma? *Am Rev Respir Dis* 1991; 143:528–532.
 - 11 Banks DE, Rando RJ. Recurrent asthma induced by toluene diisocyanate. *Thorax* 1988; 43:660–662.
 - 12 Lemiere C, Cartier A, Dolovich J, *et al.* Outcome of specific bronchial responsiveness to occupational agents after removal from exposure. *Am J Resp Crit Care Med* 1996; 154:329–333.
 - 13 Lemiere C, Cartier A, Malo, J-L, *et al.* Persistent specific bronchial reactivity to occupational agents in workers with normal nonspecific bronchial reactivity. *Am J Respir Crit Care Med* 2000; 162:976–980.
 - 14 Vandenplas O, Binard-Van Cangh F, Brumagne A, *et al.* Occupational asthma in symptomatic workers exposed to natural rubber products: evaluation of diagnostic procedures. *J Allergy Clin Immunol* 2001; 107:542–547.
 - 15 Mannino DM. How much asthma is occupationally related? *Occup Med* 2000; 15:359–368.
 - 16 Kogevinas M, Anto JM, Soriano JB, *et al.* The risk of asthma attributable to occupational exposures: a population study based in Spain. Spanish group of the European Asthma Study. *Am J Resp Crit Care Med* 1996; 154:137–143.
 - 17 Blanc PD, Toren K. How much adult asthma can be attributed to occupational factors? *Am J Med* 1999; 107:580–587.
 - 18 Arif AA, Whitehead LW, Delclos GL, *et al.* Prevalence and risk factors of work related asthma by industry among United States workers: data from the Third National Health and Nutrition Survey (1988–94). *Occup Environ Med* 2002; 59:50–11.
- Reports on an ambitious attempt to identify the relationship between the prevalence and risk factors of work-related asthma by industry in the US using survey data. The 'bottom line', how often work relates to respiratory symptoms, varies from 28.5% (workers wheeze in relation to work) and 36.5% (workers have asthma in relation to work).
- 19 Liss GM, Tarlo SM. Work related asthma. *Occup Environ Med* 2002; 59: 505–511.
 - 20 Morbidity and Mortality Weekly Report. Surveillance of work-related asthma in selected U.S. states using surveillance guidelines for state health department. California, Massachusetts, Michigan, and New Jersey. CDC surveillance summary 1993–1995. 1999; 48 (SS03):1–20.
 - 21 Banks DE, Rando RJ, Barkman HW Jr. Persistence of toluene diisocyanate-induced asthma despite negligible workplace exposures. *Chest* 1990; 97:121–125.
 - 22 Leroyer C, Perfetti L, Trudeau C, *et al.* Comparison of serial monitoring of peak expiratory flow and FEV₁ in the diagnosis of occupational asthma. *Am J Respir Crit Care Med* 1998; 158:827–832.
 - 23 McDonald JC, Keynes HL, Meredith SK. Reported incidence of occupational asthma in the United Kingdom, 1989–1997. *Occup Environ Med* 2000; 57:823–829.
 - 24 Meyer JD, Holt DL, Chen Y, *et al.* SWORD'99: surveillance of work-related and occupational respiratory disease in the UK. *Occup Med* 2001; 51:204–208.
 - 25 Kopferschmitt-Kubler MC, Ameille J, Popin E, *et al.* Occupational asthma in France: a one year report of the observatoire National de Asthmes professionnels project. *Eur Resp J* 2002; 19:84–89.
 - 26 Hnizdo E, Esterhuizen TM, Rees D, *et al.* Occupational asthma as identified by the Surveillance of Work-Related and Occupational Respiratory Diseases in South Africa. *Clin Exp Allergy* 2001; 31:32–39.
 - 27 Butcher BT, Jones RN, O'Neil CE, *et al.* Longitudinal study of workers employed in the manufacture of toluene diisocyanate. *Am Rev Respir Dis* 1977; 116:411–422.
 - 28 Ortega HG, Weissman DN, Carter DL, *et al.* Use of specific inhalation challenge in the evaluation of workers at risk for occupational asthma: a survey of pulmonary, allergy, and occupational medicine residency training programs in the United States and Canada. *Chest* 2002; 121:1323–1328.
 - Presents the results of a questionnaire detailing responses from physicians who are frequently presented cases of suspect occupational asthma. The report points out how difficult it can be to undertake inhalational challenge testing in the face of few specialized centers and an acceptance by many physicians of the 'clinical' diagnosis of occupational asthma.
 - 29 Burge PS, O'Brien IM, Harries MG. Peak flow records in the diagnosis of occupational asthma due to isocyanates. *Thorax* 1979; 34:317–323.
 - 30 Liss GM, Tarlo SM. Peak expiratory flow rates in possible occupational asthma. *Chest* 1991; 100:63–69.
 - 31 Cote J, Kennedy S, Chan-Yeung M. Sensitivity and specificity of PC₂₀ and peak expiratory flow rates in cedar asthma. *J Allergy Clin Immunol* 1990; 85:592–598.
 - 32 Newman-Taylor AJ. Occupational asthma. *Thorax* 1980; 35:441–444.
 - 33 Chan-Yeung M. Occupational asthma. *Chest* 1990; 98:148S–151S.
 - 34 Quirce S, Contreras G, Dybuncio A, *et al.* Peak expiratory flow monitoring is not a reliable method of establishing the diagnosis of occupational asthma. *Am J Respir Crit Care Med* 1995; 152:1100–1102.
 - 35 Malo J-L, Trudeau C, Ghezzo H, *et al.* Do subjects investigated for occupational asthma through serial peak flow measurements falsify their results? *J Allergy Clin Immunol* 1995; 96:601–607.
 - 36 Hankinson JL. Beyond the peak flow meter: newer technologies for determining and documenting changes in lung function in the workplace. *Occup Med* 2000; 15:411–420.
 - 37 Gannon PF, Newton DT, Belcher J, *et al.* Development of OASYS-2: a system for the analysis of serial measurement of peak expiratory flow in workers with suspected occupational asthma. *Thorax* 1996; 51:484–489.
 - 38 Baldwin DR, Gannon P, Bright P, *et al.* Interpretation of occupational peak
 - flow records: level of agreement between expert clinicians and Oasys-2. *Thorax* 2002; 57:860–864.
- Presents data comparing a computerized approach to scoring and interpreting serial peak flow rates to the interpreting of peak flow rates in the same workers with suspected occupational asthma. Data show that the experts frequently disagree in their interpretation of the meaning of the serial peak flow rates, a feature not a part of the computerized approach.
- 39 Paggiaro PL, Vagaggini B, Drate FL, *et al.* Bronchial hyperresponsiveness and toluene diisocyanate: long-term change in sensitized asthmatic subjects. *Chest* 1993; 103:423–428.
 - 40 Hargreave FE, Ramsdale EH, Pugsley SO. Occupational asthma without bronchial hyperresponsiveness. *Am Rev Respir Dis* 1984; 130:513–515.
 - 41 Banks DE, Barkman Jr HW, Butcher BT, *et al.* Absence of hyperresponsiveness to methacholine in a worker with methylene diphenyl diisocyanate (MDI) asthma. *Chest* 1986; 89:389–393.
 - 42 Banks DE. Respiratory effects associated with isocyanate exposure. In: Rom W, editor. *Environmental and occupational lung disease*. 3rd ed. Philadelphia: Little, Brown & Co.; 1998. pp. 537–563.