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The Third Jack Pepys Workshop on Asthma in the Workplace: Answered and Unanswered Questions

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The Third Jack Pepys Workshop on Asthma in the Workplace held in Montreal, Canada in May 2007 focused on emerging data, including progress over the previous three years touching on questions identified at a previous Workshop (2004). The format, based on that used in previous workshops, consisted primarily of short, thematic, structured slide presentations followed by extensive, open-ended discussion periods. The key summary content of the workshops discussions has been distilled for this account. (Expanded details of the prepared presentations in PowerPoint format can be found at: www.asthma-workplace.com.) The topics reflect an expanded scope of interest including consideration of: (*1*) work-related asthma (WRA), subsuming both occupational asthma (OA) and work-exacerbated asthma (WEA); although the latter condition is commoner than OA, discussion mainly focused on OA because the corpus of scientific literature is larger; (*2*) other related occupational airway pathologic processes, beyond WRA, including rhinitis and eosinophilic bronchitis, with focus on various methods that improve objective confirmation of these conditions; (*3*) the psycho-socioeconomic impact of WRA with presentation of questionnaires that assess disability due to OA; (*4*) development of a world-wide perspective on work-related airway disease, including the situation in countries with emerging economies where the frequency of WRA is likely similar to or even greater than that in developed countries. The overarching conclusion was that WRA and related airway conditions are underrecognized and underdiagnosed both in developed and developing countries, with a great many aspects related to personal and environmental risk, exposure, mechanisms, and assessment of impairment/disability remaining to explore to better inform primary, secondary, and tertiary disease prevention.

Presentations from, and discussion of, the Third Jack Pepys Workshop on Asthma in the Workplace; Montreal, Canada, May 17–19, 2007.

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INTRODUCTION

Work-related asthma (WRA) includes occupational asthma (OA), that is, *asthma caused by work*, and work-exacerbated asthma. The Third Jack Pepys Workshop on Asthma in the Workplace, held in Montreal in May 2007, emphasized, in particular, progress in answering questions identified at the previous, Second Jack Pepys Workshop held in 2004. Moreover, the scope of this Workshop was broadened from OA to other WRA as well, along with additional special interests in rhinitis and other work-related airway disease, the psycho-socioeconomic impact of asthma, and WRA from a global perspective, including its status in nations with emerging economies.

METHODS

Approximately 50 invited international experts from various disciplines attended the Workshop in addition to a similar number of self-registered participants. Invitees were selected on the basis of publications in the area and included those from multiple disciplines as summarized above. Following a tribute to Professor Jack Pepys and his accomplishments by Dr. J.-L. Malo, short presentations were given by internationally acknowledged experts on specific topics: Definitions and Nosological Entities, Dr. P. Blanc; Prevalence and Incidence Issues, Dr. K. Toren; Host and Environmental Interactions, Dr. D. Bernstein; Physiopathology and Mechanisms, Dr. C. Mapp; Diagnosis, Dr. J.-L. Malo; Prevention of OA: Focus on Reduction of Exposure, Dr. R. Merget; Psycho-Socioeconomic Impact of Work-related Asthma, Dr. O. Vandenplas; Treatment and Medicolegal issues, Dr. S. M. Tarlo; Occupational Eosinophilic Bronchitis, Dr. S. Quirce; Irritant-induced Asthma, Dr. P. Henneberger. Presenters were asked to review the current state of the knowledge by searching the current literature and conference presentations in their respective areas of expertise. Each topic addressed whether questions raised in 2004 during the Second Jack Pepys Workshop on OA (1) had been answered on the basis of relevant literature published since then. Content of each presentation is available on the website (www.asthma-workplace.com). Discussion of each topic followed for 1 to 1.5 hours and included additional issues still to be explored. A summary with key points was provided by Dr. A. Newman-Taylor (the topics and key points are also summarized in Table 1). These proceedings focus mainly on the content of the workshop discussion.

1. DEFINITIONS AND NOSOLOGICAL ENTITIES

These questions were posed: (*1*) How should work-exacerbated asthma (WEA) be diagnosed? (*2*) How should WRA be

TABLE 1. MAJOR TOPICS AND KEY DISCUSSION AREAS

Topic	Key Discussion Areas
Definitions and Nosological Entities	Focus on heterogeneity of work-exacerbated asthma and needs for definitions
Prevalence and Incidence Issues	Geographic differences
	Confounding of attribuatable risk by asthma prevalence
	Under-reporting and regional lack of diagnostic facilities
	Roles for age, sex, racial differences
Host and Environmental Interactions	Occupational exposures during pregnancy
	Studies needed for gene–environmental interactions
	Useful role for genetic studies in pathogenesis
	Increasing role for less traditional exposures in work-related asthma
Physiopathology and Mechanisms	Possible T-cell response in hairdressers with OA
	Nonlinear exposure–response relationships and tolerance
	Effects of basophils and monocytes in pathogenesis
	Airway remodeling when asymptomatic
	Possible role for low-level irritant exposures
Diagnosis	Diagnosis and relevance of occupational rhinitis
Prevention of Occupational Asthma: Focus on Reduction of Exposure	Pre-marketing testing of chemicals
	The warning role of occupational rhinitis
	Exposure controls to prevent work-exacerbated asthma
	What is an acceptable exposure risk?
Psycho-Socioeconomic Impact of Work-related Asthma	Direct and indirect costs of OA and WEA
	Psychological outcomes
Treatment and Medicolegal issues	Variability of different compensation systems
	Relatively poor average asthma outcome
	Importance of prevention
Occupational Eosinophilic Bronchitis	Lack of correlation of clinical severity and sputum eosinophil counts
	Time-course of eosinophil responses on challenge
	Compensation issues
Irritant-induced Asthma	Differences from work-exacerbated asthma
	Classification of asthma among cleaners
	Association with vocal cord dysfunction
	Multiple roles for workplace irritants

classified when symptoms are induced by conditions encountered in the workplace but that may also be more ubiquitous (for example, aeroallergens) or that might induce symptoms in the presence of otherwise asymptomatic airway hyperresponsiveness (AHR)? (*3*) Do some reports of WRA symptoms occur from a subset of workers who have underlying mild and asymptomatic AHR before working rather than the induction of AHR by work exposures? A few published definitions of WEA, also known as work-aggravated asthma (2–5), were presented, showing heterogeneity in classification. The clinical manifestation is usually that of pre-existing asthma that is symptomatically worse at work, but less commonly it can present as apparent new-onset asthma and can mimic OA. Incidence was compared with OA, showing that it is at least as common as OA, and several studies on the clinical manifestations and social consequences of WEA were reviewed (6–17) showing significant socio-economic impact from WEA, in some studies similar to that of OA. Difficulty in classification was illustrated by a case with a recurrence of previous childhood asthma while working: the audience was divided as to whether this was unrelated asthma, OA, or WEA.

Points Raised in the Discussion

WEA, like asthma, is heterogeneous. It can sometimes be difficult to distinguish from OA, but there is a vast spectrum of WEA cases, ranging from cases with investigations similar to OA but having negative specific inhalation challenges to the other extreme, of subjects who miss work for a few days because their asthma gets worse, who are not seen by specialist physicians, and who have limited investigation.

Opinions on the diagnosis of WEA ranged from reliance on symptoms alone, to the need to develop a tight, clear definition. An ATS panel is developing a document on WEA that may clarify this; however, definitions vary according to their purposes and there might be more than one needed. There should be a clear basis for pre-existing asthma before the exacerbation. Clear definition might be more important for medicolegal purposes than for public health purposes, and the first efforts should be for the former purpose. Although aggravation or exacerbation of asthma at work cannot be confirmed in an acute or subacute situation (days or weeks at work), nevertheless, with a longer period of symptoms, there could be work-related changes documented. In the same way that criteria were proposed for defining exacerbations of chronic obstructive pulmonary disease, there should efforts to define the more subtle entity of asthma aggravation. There can be more difficulty assessing aggravation in epidemiologic studies because cases can include incident cases with persistent symptoms as well as those with relapsing symptoms.

Better identification of the nature of the exacerbating triggers was suggested. Mechanisms for worsening asthma should be examined in the context that irritant triggers may vary for the different symptoms such as cough, wheezing, and shortness of breath.

2. PREVALENCE AND INCIDENCE ISSUES

Vocational cohorts (18, 19) have practical preference over birth cohorts. Focus should be put on exposure differences that may explain variations in frequency between different countries. There should also be separate analysis by sex: for example, in Finland excellent examination on the risk of occupation on the incidence of asthma has been performed from data of three national registers that showed different risks for men and women (20). An important prospective study, the European Community Respiratory Health Survey (ECRHS) that started around 1990 (21), showed quite a high attributable risk fraction for asthma due to occupation: 10 to 25% (22). Problems of epidemiologic studies include: misclassification due to the overlap between asthma and other chronic obstructive lung diseases; attribution bias in responses to questions on symptoms after starting exposure; varying symptoms, as workers may experience chest or nasal symptoms without wheezing; and cultural issues that may also affect the frequency of reporting postnasal drip or vocal cord dysfunction symptoms.

Points Raised in the Discussion

The geographical distribution of asthma, with greater prevalence among English-speaking countries, was discussed. A geographical pattern occurring within different areas of the same country is also likely to also be present for OA. Data from the ECRHS survey (22) showed large variations in prevalence of sensitization to ubiquitous allergens in Spanish and French cities as well as variations in the attributable risk of asthma due to sensitization. Data were also presented on the positive relationships between the prevalence of exposures and prevalence of symptoms of asthma. The attributable risk for asthma due to occupations is less in countries with higher prevalence of asthma, the explanation being that for the same amount of OA the less total asthma there is, the more attributable risk there is for occupation. The issue of underreporting was addressed, as was the issue of insufficiency of access to simple and efficient

objective testing in developing countries. Comparison of prevalence between countries is important; there are similarities in the frequency of work-attributable asthma for some jobs, such as cleaners. Data from South Africa and Brazil taken from sentinel-based studies have shown relatively low risks of OA, incidence less than 2 per 100,000 in contrast to almost 12 per 100,000 in Finland (23). Rates of asthma are higher in women, older individuals, and those with a past history of tuberculosis (the mechanism of this was questioned, since it might be expected to be protective for IgE-mediated sensitization) and are affected by type of occupation. Education also plays a significant role, WRA being commoner in workers with only a primary education.

The effect of sex was discussed. Most surveillance data are not stratified by sex. Some sex differences are reported (24), although many apparent differences could relate to different exposures. Data on asthma caused by snow-crab showed that both sex (being a woman) and having greater exposure levels were associated with probable OA (25).

Several aspects related to the severity of asthma were discussed. A study from France showed that asthma related to occupation was generally more severe (26). An Italian multicenter study showed that severity of OA did not relate to the specific agent. A bigger problem perhaps is in the control of asthma (27).

Many pediatricians think that asthma is a childhood disease only and cannot start later in life. Studies should examine incident asthma, the respective roles of new asthma in adults and of relapse of childhood asthma, and how exposure in the workplace affects each of these conditions. Birth cohorts could be useful in regards to OA, particularly in understanding whether or not there has been previous childhood asthma. Both studies in occupational settings and general population studies should be done. These studies should also include questions related to factors (such as previous asthma) that might influence teenagers and young adults to select specific jobs.

3. HOST AND ENVIRONMENTAL INTERACTIONS

Ethical concerns and needs for care and safeguards about profiling workers for genetic and other risk factors, therefore possibly restricting work options, were discussed. Determinants of WRA that have been explored include: atopic status, exposure, the role of prior sensitization, airway hyperresponsiveness, occupational rhinoconjunctivitis, genetic factors, and smoking (28–31). Questions remain: (*1*) Is early evaluation of risk factors in individual exposed workers feasible or useful? (*2*) Should we pay more attention to defining exposure–response relationships? (*3*) Given the limitations, how can we better define gene–environment interactions in OA? A more holistic approach is needed, one that includes examination of other environmental factors in their interaction with occupational and genetic factors (e.g., pets, indoor allergens, biocontaminants, infection, etc.).

Points Raised in the Discussion

Onset of atopic diseases of children may be affected by occupational exposures during pregnancy (32). The issue of the intersection of different risk factors, including the effect of irritant exposure on sensitization, was raised: can repeated irritant exposures influence the onset of atopy?

Detection of exposure–response relationships is complex. Epidemiologic studies in the field of WRA have been performed in small samples; therefore, significant associations are difficult to detect. The exposure assessment is generally performed using simple methods and shows great variability in levels of exposure. Combined studies should be done to increase power of studies of gene–environment interactions.

Genetic studies were suggested to be currently more useful to elucidate pathogenesis than risk factors. Genetic differences in metabolic enzymes related to redox homeostatis that are being assessed include GSTP-1, GSTM, glutathione peroxidase, NADPH oxidase, and SOD2 superoxide dismutase. Some polymorphisms were associated with isocyanate-induced antibody response; another gene candidate is chitinase. Single nucleotide polymorphism (SNP) gene chips that allow for screening of thousands of SNPs at the same time might be useful in OA (33).

The need to examine genes in identifying workers at risk of OA was questioned. Factors such as atopy and smoking have been studied and do not have any effect on the selection of career by students. Control of OA by reducing exposure should be prioritized.

Gene–environment interaction was examined in relation to specific causes of OA (34). The presence of the minor G allele of TLR4 bears a positive association with laboratory animal sensitization and a negative association with chest symptoms due to laboratory animals. CD14/-1619 GG alleles were associated with lower FEV_1 (percent predicted). These genetic results support the investigation of endotoxin as a relevant modulatory exposure in the laboratory animal workplace. Identifying genes of interest based on specific relevant exposures, rather than on disease outcomes, may be more effective in clarifying gene–environment–disease interactions and mechanisms of OA.

In Finland the role of traditional sensitizers in causing OA is diminishing, but there is an increased role of other exposures for work-related asthma: passive smoking, indoor molds (35), and plastic raw material (36).

Recent results of the ECRSH have shown the role of atopy and parental asthma in asthmatic symptoms related to the workplace (22). The role of irritant exposure is demonstrated by studies performed in cleaners (37).

The expression "candidate interactions" was proposed, meaning that the interaction is candidate: if there is information on the function of the gene, one might look for the environment; and if there is a hypothesis of the function of environment, one might look for the gene, this representing a back-and-forth story. Workers in the field of environment should be as ambitious as geneticists, who include thousand of genes on SNPs, by examining numerous environments. There was support for this idea in examining the role of genes in workers exposed to irritants (cleaners) and organic compounds (microbial and allergen exposures in farmers). Racial differences were discussed: the genetic associations found in occidental isocyanate workers were not confirmed in Korean workers. Moreover, the genetic associations may vary depending on the types of isocyanates (viz., TDI and MDI).

The ideal appropriate control group was also considered: workers with similar exposure or no exposure?

4. PHYSIOPATHOLOGY AND MECHANISMS

The following aspects were highlighted: the heterogeneity of asthma (38–41); the different timing of asthma, airway inflammation, and hyperresponsiveness (42, 43); the possibility that skin absorption leads to respiratory sensitization for some agents (44); are animal models useful in understanding the pathogenesis of OA? Is the pH of bronchial secretions relevant (45)? Is the mechanism of diisocyanate-induced asthma IgE-mediated (46–48)? Is the concept of "united airways" appropriate? To what extent is rhinoconjunctivitis a risk factor for high-molecular-weight–induced OA? What is the role of CD8 in the physiopathology of OA (49)? What is the mechanism of OA due to persulfate in hairdressers (50)?

Points Raised in the Discussion

Data in hairdressers show some with positive inhalation challenges to ammonium persulfate; a significant increase in sputum eosinophils was seen after challenges; there was no increase in neutrophils; there were also changes in nasal lavages (51). Seven of 24 challenge-positive patients had a positive patch test, suggesting a T cell–mediated response (51). Another Spanish center noted increases in induced sputum eosinophils, but some subjects had increased neutrophils; 20% had positive skin prick tests to ammonium persulfate.

Tolerance to occupational allergens was discussed. On exposure to rats, IgE sensitization is lessened at the high-exposure end, whereas specific IgG and IgG_4 antibodies and IgG_4/IgE ratio levels are proportional to exposure (52). Developing specific IgG and IgG_4 offer "natural tolerance" against work-related chest symptoms. Contrary to the situation of exposure to laboratory animals, a Th2 response does not seem to operate in diisocyanate-induced asthma.

There is an increase in activated basophils obtained from induced sputum in subjects challenged with low-molecular-weight agents in the same way as for IgE-mediated asthma. Basophils can be activated by a non-IgE mechanism (53). The activity of monocytes in diisocyanate-induced asthma was discussed. Monocyte chemoattractant protein-1 (MCP-1) production has a better correlation with diagnosis than specific antibody levels has, especially in workers remotely removed from exposure (54). MCP-1 and specific IgG responses remained after cessation of exposure (55).

Results of bronchial biopsies in workers with OA and apparently cured more than 10 years after cessation of exposure were presented, showing increased density of ECP- and TGF-β–positive cells, a reflection of persisting inflammation, and subepithelial fibrosis, a feature of remodeling (56).

An analogy was proposed between OA and occupational dermatitis that can be allergic or irritant, both being of latent intervals and having individual susceptibility. Therefore, it was suggested, irritant-induced OA with latency may exist and may include those without sputum eosinophilia and with high sputum neutrophilia. According to experience in Montreal, 60% of workers with OA do not have increased numbers of sputum eosinophils, and the presence of eosinophils does not relate to the causative agent, atopy, latent interval, or duration of exposure. However, workers with eosinophilia had more severe disease. A hypothesis was proposed that low-level irritant exposures may cause OA with a latent period.

5. DIAGNOSIS

Some questions raised at the 2nd Jack Pepys symposium require further answers: How can simple diagnostic tools be applied, used, and validated in regions where no specialized diagnostic facilities are available? Are specific inhalation challenges with occupational agents and other testing for WRA safe, readily available and of a high-quality standard? The infrequency of use of the occupational history and the value of symptom components were addressed (57, 58). Objective confirmation of OA is still too rarely performed, and physician's agreement on diagnosis is poor (59). Other presented topics were diagnostic investigations in WRA (9, 55, 60–64), barriers to an early diagnosis (65), economic risk factors (8), severity (26), and British guidelines (66). Rhinoconjunctivitis is often associated with OA, but functional and inflammatory tests of occupational rhinitis (67–69)are not standardized.

Key issues are that: (*1*) confirmation of OA is often lacking; (*2*) sophisticated tests (induced sputum, specific inhalation tests) should be used more often; (*3*) between-physician agreement on diagnosis is not satisfactory; (*4*) diagnosis takes too long; (*5*) guidelines should become practice; (*6*) nasal involvement should be examined, preferably by objective testing.

Points Raised in the Discussion

Occupational rhinitis was the focus of discussion; aspects to be explored include (*1*) the relationship between bronchial and nasal involvement, and (*2*) differences in involvement related to the type of occupational agents. Approximately 10% of subjects with occupational rhinitis develop OA (70).

Danish studies on acoustic manometry in animals were presented (71) discussing the physical principles based on sound waves with generation of a surface area and a two-dimensional production of a volume. Changes in nasal volumes by acoustic rhinometry after specific allergen challenges show a 25% drop to be a sensitive and specific threshold. Histamine and prostaglandin D-2 challenges do not show a clear distinction between responses of subjects with and without rhinitis (72).

In the use of acoustic rhinometry in workplace studies, the importance of examining the same worker over time was stressed, since cross-sectional studies are not informative. Studies among bakery workers showed good correspondence between symptoms and changes in acoustic rhinometry (73). Nasal biopsies were suggested to yield better information than nasal lavage, since the methodology for nasal lavage is still not easy or well established.

The irritative effects of fumes and aerosols of bitumen on the airways by cross-shift assessments were discussed. A German study found changes in nasal lavage samples only in a high-exposure group with a small increase in neutrophils but not in IL-8 (74).

A document on occupational rhinitis prepared by a task force of the European Academy of Allergy and Clinical Immunology was summarized (69). The word "rhinitis" reflects inflammation only, but many patients have vasomotor rhinitis with nasal symptoms triggered by physical factors that do not involve an inflammatory component. Workers may be exposed to various physical factors at work and have symptoms related to vasomotor rhinitis. Some subjects who report symptoms of hayfever have no evidence of systemic specific IgE production. Local production of specific IgE is possible in this instance, and perhaps this may occur with high-molecular-weight occupational agents. It is not known if specific inhalation challenges may induce positive reactions in these workers.

Few data are available on population-attributable risk of occupational rhinitis; a study in France found a relative risk of 1.5 for vapors, dust, and fumes in causing rhinitis (75). However, the validity of epidemiologic data on attributable risk of occupations in regards to rhinitis was questioned, since the causal relationship is not sufficiently well identified. Assessing attributable risk of occupation on rhinitis would represent a second step of epidemiologic studies.

6. PREVENTION OF OCCUPATIONAL ASTHMA: FOCUS ON REDUCTION OF EXPOSURE

Five relevant research questions were identified in which substantial progress has been made, and an additional question identified, to be addressed in future studies.

In 2002, the main practical constraint for developing occupational exposure limits for high-molecular-weight sensitizers was thought to be the lack of well-standardized immunoassays for evaluation of allergen exposure in the field (76). Information was reviewed for wheat allergens (77–79), showing that there has been progress in assessing dose–response exposures to

wheat flour, and relationships to specific sensitization (79), but a recent European Expert Committee was unable to recommend specific exposure limits.

Primary prevention of OA can be achieved by exposure control rather than substitution with nonsensitizing products. For OA from natural rubber latex (NRL) glove use in healthcare workers, studies support an effective role for substitution (80, 81). Complete avoidance/substitution may be feasible for some sensitizers, such as enzymes in flour (82), complex platinum salts as catalysts, and for some uses of acid anhydrides. Technical modifications to formulate isocyanates with very low monomeric content may reduce risks of sensitization, but require further study. In contrast, it is unlikely that there could be complete or near-complete occupational avoidance of sensitizers such as laboratory or farm animals, so for these, as well as most sensitizing agents, exposure reduction will likely continue as the only option. Precise labeling of compounds as sensitizers, such as enzymes in flour, was considered appropriate. Simple workplace assays of allergens such as fungal amylase (83) may facilitate improved workplace exposure management.

Diisocyanate exposure assessment was discussed, and has been measured in areas of tasks adjacent to spray painters (84). To assess polyisocyanates, measurement of total isocyanate group may be the most practical and feasible metric for research, control, and regulatory purposes (85) but biological measures in urine and plasma samples also could prove useful for exposure assessments (86). There is concern, mainly from animal studies, as to the potential risks of skin exposure and the importance of preventing such exposure (44).

An evidence-based review of the management of OA (87) found that there are very few studies on the consequences of reduced exposure to a work sensitizer after diagnosis of OA, rather than complete removal, and this should be further determined.

Points Raised in the Discussion

Questions raised: Will new European regulations on chemical testing before marketing address allergenic/sensitizing potential, and if so, may this serve as a model for other countries? Is it still relevant to discuss underlying atopy in the context of prevention, since it does not affect current interventions? Should the development of occupational rhinitis be used as an intervention marker in preventive measures for OA? Which components of secondary preventive measures are most effective and at what frequency/time window should they be used? What are the best assessment tools to evaluate preventive measures? Have we overlooked the value of overwhelming ecological evidence (e.g., the temporal studies of associations with changes in NRL use) by expecting controlled epidemiologic studies? What are the preventive effects of reducing dust/fume/vapor exposures for OA, work-exacerbated asthma, and development of asthma?

General discussion on the aim to identify exposure levels that protect *most* workers from sensitization concluded that there must be a decision reached as to what is an *acceptable* risk, but it is not yet known how to decide this. Often a single specific sensitizer is not identified (e.g., in high-risk occupations such as domestic cleaning, mining, agriculture), and there may be important "new" sensitizers that have not been identified and studied. Workers may be reluctant to even seek medical attention for fear of loss of job and income, or may simply leave for other work without investigation. Additional factors playing a role may include the role of stress in asthma, risks from a low socio-economic geographic area and socio-economic status, and possible effects of air pollutants. The importance of improving knowledge by primary caregivers was noted, since they may be the sole health care provider.

For workers exposed to isocyanates, preliminary results of a Quebec study of surveillance appeared to show beneficial effects in outcome of asthma.

7. PSYCHO-SOCIOECONOMIC IMPACT OF WORK-RELATED ASTHMA

Since the American Thoracic Society Guidelines (88) for rating impairment from asthma were published in 1993, newer validated instruments for assessing asthma control (www.qoltech.co.uk, www.qualitymetric.com) and newer treatment guidelines for asthma (www.ginasthma.com) have been published, so consideration should be given to updating the impairment rating guides. Assessment to rate "permanent impairment" may be most optimally performed 2 to 5 years after diagnosis (89).

Sputum eosinophils correlate well with ATS criteria for levels of impairment (90), although a component of airway inflammation can persist despite normal functional tests (91) and it is not known if this is associated with subsequent morbidity.

One study (92) has shown lower quality of life (QOL) in those with OA after removal from the causative exposure agent than for other asthmatics when matched for asthma severity. Chronic work-exacerbated asthma has been reported to produce similar income loss and unemployment as OA on follow-up (93) and both are common. A Finnish study found better QOL if there was current employment and milder asthma (94). Psychogenic factors can play a role in QOL for OA, and significant frequency of anxiety and depression has been shown (91). Investigation is needed to determine the effects of interventions such as rehabilitation/retraining on these psychogenic responses.

Economic impact of work-related asthma should consider not only direct (health care) costs, but indirect costs from impaired work productivity and compensation/rehabilitation costs, as well as the intangible costs from reduced QOL (for the latter there are no data). Income loss is more likely when there is avoidance of exposure that leads to a change of job. In Europe, less than 20% with OA are relocated within the same company (95), compared with 31% in Quebec (96). In one study, only 22% of compensated workers reported that their income loss has been offset by compensation (97), and in many European countries compensation does not include rehabilitation/retraining, perhaps accounting for the relatively high proportion (30%) of workers who continued to be exposed to the causative agent (97). Therefore, at least in countries where work-disability remains the major determinant of the impact on socio-economic status and QOL, more should be considered in compensation than the lung function impairment and optimal asthma treatment.

Points Raised in the Discussion

In Quebec the costs of permanent disability compensation and retraining for OA are now on average $75,000 per case (98). UK lifetime cost per case (direct and indirect but not including intangible costs) are estimated to be £150,000, of which 47% is borne by the patient/worker, 47% by the state, and only 4% by the employer, suggesting little incentive for the employer to provide support or preventive measures. In a U.S. primary care study, health care costs for those with work-exacerbated asthma (WEA) were similar to costs for those with other non–work-related asthma, but the WEA group had worse QOL (99). Studies are in progress to determine the prevalence and impact of anxiety disorders, mood disorders (depression), and hypochondriasis among those with suspected OA prior to a confirmed diagnosis.

8. TREATMENT AND MEDICOLEGAL ISSUES

Current management of OA was reviewed. A systematic review (100) was unable to perform group statistical analyses of published studies due to vagaries of reporting, but graphic display of studies suggested better medical outcomes for sensitizer-induced OA with removal from the relevant workplace exposure, as is generally advised. Nevertheless, for socioeconomic reasons, some workers continue to have some exposure to a relevant work sensitizer (101). Minimal potential exposure to some relevant allergens such as natural rubber latex (NRL) in low protein, powder-free gloves used by coworkers in the same area as a worker with NRL-induced OA appears to be a safe procedure (102), but there are little similar data for other work sensitizers (103). There is very limited information as to possible benefit from immunotherapy or monoclonal anti-IgE antibodies to reduce severity of responses to a work allergen (104–107).

Careful medical monitoring for workers with sensitizer-induced OA who may have further exposure to the sensitizer was stressed. Information on agents that may cross-react with occupational sensitizers and trigger asthma is limited. Potential reasons for poor medical outcome of OA despite removal from the job exposure were discussed.

Compensation and medicolegal issues vary widely in different countries and within countries. There are no published data as to the extent to which the compensation process might contribute to persistence of asthma/disability; potential factors may include lack of eligibility for compensation, avoidance of initiating a claim due to fear of job or income loss, or delays in claim decisions. The process in Ontario was discussed as an example of a compensation system.

Points Raised in the Discussion

Discussion included some comparisons between the more comprehensive compensation systems from Ontario and Quebec, which are funded by annual employer premiums and include a component of retraining and prevention, in contrast to the Statutory Compensation system in the United Kingdom which, it was reported, does not include rehabilitation/retraining or income replacement. Workers in the United Kingdom have an option of filing a suit under common law, but even if successful may actually receive only a minority of any award. It was stated that over a third of workers with OA claims are unemployed 3 to 5 years later, with serious financial results. The system in the United States was also reported to be difficult for workers to navigate, such that workers may fail to declare their work-related symptoms and continue to have the same work exposures. Some Canadian provinces also provide relatively low compensation, which is a deterrent to reporting, and some are not involved in preventive measures. The psychosocial stress of job loss and income loss was emphasized and the suggestion made that resulting depression could contribute to poor compliance with asthma medications and to co-morbidity.

The relatively small proportion of workers with OA whose asthma clears after removal from exposure was illustrated in Quebec diisocyanate workers (108). There is a need to identify if there are workers who might have a similar outcome by staying at work with reduced exposure. In other studies, those who had an eosinophilic response on specific challenge were more likely to improve after removal from exposure.

Discussion returned to prevention of OA as being most preferable, and debate ensued as to possible incentives for industries to enact exposure-control measures and, as a less preferable option, to have deterrents for companies in whom cases of OA occur—at the least it was suggested that they should bear most/all of the costs of adequate compensation, income replacement, and retraining.

9. OCCUPATIONAL EOSINOPHILIC BRONCHITIS

Eosinophilic bronchitis, both as in relation to OA (109) and as a separate entity, was described. Eosinophilic bronchitis as a syndrome without airway hyperresponsiveness (110) can be nonoccupational (111) or occupational. An example of occupational eosinophilic bronchitis was given (112) and diagnostic criteria reviewed (113).

In addition, the cough response to inhaled capsaicin is increased and unlike asthma, mast cell infiltration of airway smooth muscle is absent (114). Pathogenic mechanisms are unknown, but data suggest an increase in activated eosinophils, basophils, and PGE_2 in sputum of subjects with eosinophilic bronchitis compared with subjects with asthma and control subjects, while LTC_4 levels were intermediate between the other two groups. Occupational case reports have included many sensitizers that are recognized to cause OA. Therefore, eosinophilic bronchitis should be considered in the spectrum of work-related airway diseases (115) and induced sputum performed in conjunction with other diagnostic tests during a period at work and off work as well as pre- and post-specific inhalation challenge tests.

Recent cough guideline recommendations relating to eosinophilic bronchitis were reviewed (116). Follow-up of patients with eosinophilic bronchitis (not necessarily occupational) over a mean of 3 years showed that a subset develop overt asthma and/or airflow limitation, and only a minority resolve (117). The outcome of occupational eosinophilic bronchitis needs to be determined.

Since not all individuals with asthma have eosinophilic bronchitis, and not all with eosinophilic bronchitis have asthma, there is a need to rethink airway diagnostic categories as the phenotype in a patient may depend on both the trigger and host factors as suggested by Wardlaw and coworkers (115).

Points Raised in the Discussion

It was suggested that the diagnostic term eosinophilic bronchitis (EB) should not be used for those who develop increased sputum eosinophils after specific challenge but do not have associated symptoms or pulmonary function changes. There was agreement that a cough must be present for the clinical diagnosis, but the extent of cough does not correlate well with the percentage of sputum eosinophils (117).

A study of 67 workers in Belgium who underwent specific challenges with occupational agents was discussed. This showed that an increase in sputum eosinophils of 2% or more represents an early and sensitive but not specific marker of subsequent bronchial response to occupational agents, suggesting that sputum eosinophilia should be systematically assessed after specific inhalation challenges in the absence of changes in FEV_1; a significant increase in sputum eosinophils means that further challenge exposure in the laboratory and/or at the workplace is needed before excluding the diagnosis of OA. Exhaled NO increases 24 hours after specific challenges (118, 119), although preliminary findings suggest that it does not seem as sensitive as induced sputum. The standard criterion of FEV_1 used to assess lower airway specific challenge responses was questioned, since other criteria like inflammatory mediators do not clearly show the same time course of reactions.

It was suggested that the guinea pig models may support EB as a precursor of asthma, but others responded that the EB phenotype is stable—only about 10% develop asthma, and there is more chance of developing fixed airflow limitation. One participant noted how surprising it is that occupational EB

is not diagnosed more frequently (only one or two such patients per year in that specialist's practice). Even after removal from work, they seem to have episodic exacerbations. The topic presenter stated he has seen about 20 patients with occupational EB, but this may reflect a referral bias. The question of compensation for these patients was raised, and no policy for this is known. Increases in serum ECP in response to specific challenge, even without an increase in eosinophil counts, were noted in South Korea (120), but not by the presenter in a consistent way in sputum assays (he has not, however, compared this with serum levels). The association with rhinitis was discussed: most patients with EB have rhinitis, and conversely patients with rhinitis may have eosinophils in the airways without cough or asthma. There is a need for better understanding of reasons for neutrophil versus eosinophilic responses in individuals with asthma.

10. IRRITANT-INDUCED ASTHMA

Two relevant questions from the previous workshop concerned host factors and biomarkers in irritant-induced asthma, especially for cases that do not completely fulfill criteria for reactive airways dysfunction syndrome (RADS). Previous studies have examined the interaction of irritants and allergens. A report of "not so sudden" irritant-induced asthma (121) noted the significant contribution of underlying atopy and/or asthma, while conversely, irritant exposures may increase the allergic response (122), as shown with formaldehyde in subjects with asthma undergoing allergen challenges (123), perhaps by inducing an increase in airway permeability. An adjuvant effect of *inhaled* quaternary ammonium compounds has been suggested in mice for sensitization to *subcutaneous* ovalbumin (124). Previously observed associations between professional domestic cleaning and asthma have been extended observing that the odds ratio for asthma was increased with moderate or frequent use of bleach at work (30). In the nonoccupational setting, children in areas with more chlorinated swimming pools had an increased risk of asthma (125), and lower serum levels of Clara Cell-16 protein among children who swam frequently in chlorinated pools suggest possible damage or dysfunction to Clara Cells. No association of such exposure with exhaled nitric oxide has been found (126, 127), but increases were seen in serum alveolar cell proteins with increased pool attendance among children and adults (128). A further study of adults with asthma showed an asymptomatic increase in airway responsiveness after spending time in a chlorinated whirlpool (129). Conclusions were that in some studies host factors have modified the effects of exposure to low-level irritants, and biomarkers of effects continue to be explored.

A new/modified question was proposed: What proportion of non-RADS work-related asthma is due to low-level irritant exposure (*1*) alone, (*2*) in the presence of atopy, or (*3*) combined with allergen exposure? Irritants may disrupt epithelial structure, making it easier for allergens to cross the epithelium, followed by sensitization to workplace agent and asthma.

Points Raised in the Discussion

Asthma related to nonmassive irritant exposures may represent symptomatic recurrence of asthma in workers with previous asthma that had become asymptomatic. This should be classified as work-exacerbated asthma. Of note, about 5% of the "normal" population has measurable airway hyperreponsiveness. Also, there is some host variability, through poorly understood mechanisms, even in response to agents that are not allergens/sensitizers. The term "irritant" needs better definition in this context.

A cough may result from an "irritant" exposure releasing neuropeptides and increasing the sensitivity of nonmyelinated C-fibers in the airways below the tight junctions. Transient receptor potential vanilloid can be stimulated by heat, a low pH, capsaicin, and some irritants. The capsaicin response was noted to be greater in women, and development of asthma in cleaners was mainly in women. However, others felt that the epidemiologic classification of asthma in cleaners was likely to be truly asthma, since the questionnaires used were well validated. Within the term "work-exacerbated asthma," does "permanent exacerbation" exist? Could this result from a RADS-like exposure in a worker with pre-existing asthma? The outcomes in such workers have not been well described.

In models of cleaners, it was noted that accidental exposures are always significant; workers may have had an initial accidental exposure and following that may have work-exacerbated asthma. In a Denver practice to which railroad workers are commonly referred, several have RADS followed by persisting vocal cord dysfunction or upper airway syndrome (130): should the term "irritant-induced united airway disease" be used?

Some discrepancy is seen between agents reported to cause asthma in population studies and from specialty clinics, perhaps due to differences from populations in general practice. The possibility that asthma may be incorrectly attributed to irritants was considered (e.g., for swine workers who have exposure to pig allergens as well as irritants). In addition, it was noted that in some studies quaternary ammonium compounds have been used as an example of irritants, although benzalkonium chloride has also been reported to be a sensitizer. The effects of some "irritants" may be more specific than others (e.g., diesel fumes can have an adjuvant role also).

WORKSHOP EXECUTIVE SUMMARY AND BOTTOM-LINE ISSUES

- The strengths of this Workshop include representatives from multiple disciplines, from basic science, environmental science, epidemiology, occupational hygiene, and clinician researchers.
- The international participation reflects WRA as a worldwide concern, although still understudied in many developing countries. It is a potentially preventable and curable problem, important for public and occupational health, and the outcome of research has potential for policy changes.
- WEA and OA represent important clinical problems, and patients need as *accurate* a diagnosis as feasible with support for best management and future occupation; misdiagnosis can be as harmful as missing the diagnosis, leading to inappropriate advice to change a job with potentially adverse financial and social consequences.
- WEA is common, but further consensus is needed as to clinical and research definitions and diagnostic criteria.
- OA is a valuable model for non-OA, having a clearly defined single specific causative agent.
- Definitions need to be clearer to allow valid comparisons between studies. The concept of work-reactivated asthma seems useful. For the phenotype of eosinophilic bronchitis, it remains unclear whether this is a different disease or a different stage of asthma.
- None of the current diagnostic tests for OA is perfect in isolation. If new tests are added, such as induced sputum

eosinophils, it is important to have studies to determine the diagnostic gain from these before adding or substituting them for other tests.

- Patients studied from tertiary centers may not represent the full spectrum of disease, and can have more psychiatric/psychological co-morbidity than in primary care settings. There is a need to balance the medical and socio-economic impacts of job changes for workers with OA.
- The potential of markedly reduced exposure, as has been successful for OA from natural rubber latex in allowing sensitized healthcare workers to continue to work, should be investigated.
- Physicians need to consider, and influence, compensation systems to provide appropriate support and retraining for workers with OA.
- A major advance in recent years has been the understanding that the OA incidence due to sensitizers largely relates to the exposure levels. Workplace controls should focus on reduction of exposure rather than worker susceptibility in the prevention of OA. In that light, we now need well-performed intervention studies to demonstrate effects of preventive measures and means to implement them widely and to enable change. There is a need also to increase employer and government commitments to prevention and appropriate compensation, and a need to be able to ensure preventive measures.
- Genetic studies may provide helpful data, insofar as gene–environmental interactions may be relevant to mechanisms of disease. Relative to idiopathic disease, the population with OA due to high-molecular-weight antigens has a well-defined phenotype, set of exposures, and sensitizer-based mechanism of disease. The disadvantage of relatively small sample size could be overcome by collaborative studies using hypothesis-generating and hypothesis-testing analytic strategies.
- Mechanisms of sensitization remain less clear for many low molecular weight sensitizers, such as diisocyanates. Further understanding may lead to better immunologic testing that could be relevant to exposure assessment, diagnosis, and disease management. The role of irritants in asthma causation and exacerbation, acting alone or as adjuvants or co-factors, also requires more research.
- Large knowledge gaps exist in work-related rhinitis and in global aspects of WRA and related disability.
- Finally, the need for research addressing work-related asthma was particularly glaring, not only to advance knowledge in this area but also to attract the best young researchers for the future.

This official conference proceedings was developed by an *ad hoc* subcommittee of the Environmental and Occupational Health Assembly.

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