Epidemiologic Methods for the Study of Occupational Asthma*

Current Problems and Solutions

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As its very best, epidemiology is a woefully inadequate scientific discipline, reliant on observational tools to discern order in the chaotic and undisciplined “experiments” of nature and society. Perhaps no area of modern research so stresses this inherent weakness than the study of occupational asthma. The end point is surprisingly elusive; host factors, as yet undefined, play havoc with dose-response relations on which we traditionally rely and, as if these were not trouble enough, the disease itself frequently impacts exposure through job selection and behavior. Yet without relevant animal models for the most part, we have little choice than to make the most of it.

Over the past 2 years, I have begun to turn my attention to two of the more prominent problems in this field—iso­cyanates and so-called potroom asthma—after some years dabbling with easier occupational health problems. It has been a humbling experience, but one that has hopefully afforded me an opportunity to look at old problems with new eyes, both to marvel at the successes of many who have contributed so greatly to our current understanding and to consider how further progress may be fostered. With apologies for those for whom this may all be rather obvious, my goal in this article is to provide a simple road map to the traps and pitfalls I have discovered during these incipient efforts, and some of the landmarks that have served as guideposts along the way.

What Are the Questions?

Let me start with a review of the most obvious issue confronting investigators in this field, and one that has proved surprisingly thorny: an articulation of the questions. A primary goal with most epidemiologic investigations in occupational health is the establishment of etiologic relationships between an environmental agent and a health outcome of interest. Once established as a cause, control strategies demand attention to dose-response relationships, with attention only very late turning to host factors, secondary prevention, effects of medical treatment, and the like. Since at-risk populations are usually well defined in occupational settings, overall impact on the general population and control strategies that rely on efforts outside the workplace are rarely subjects for research.

Ironically, establishment of the etiologic relationship between a specific exposure and asthma is not a major challenge for the epidemiologist. Because of the self-limited nature of single exposures, controlled human experimentation, also known as specific bronchoprovocation challenge, has proved the most satisfactory approach to accomplish this. However, epidemiologic observations may be hugely important in pointing the direction toward the identity of possible agents for such challenge, one of the current goals of efforts to understand potroom asthma.1,2 Dose-response relationships, the bulwark of occupational cancer research and investigations of direct-acting toxins, give way in the asthma domain to efforts to characterize setting, circumstances, and forms of exposure leading to risk, and crucial effort to understand the elusive basis for idiosyncrasy in the exposed populations. Recognizing that control of exposure may not prove as adequate to control disease as has been successful with other hazards,3 the importance of natural history and the effects of medical intervention have become central research themes.4,5 Broad public health questions are raised because of the sheer numbers of causal agents,6 the ubiquity of some in diverse workplaces, and the growing asthma epidemic in the population.

This most peculiar list of questions, summarized in Table 1, would appear to offer a manageable perspective for discussion of some current problems investigators face. In view of space limitations, I will focus on several very thorny ones.

What Are the Problems?

All etiologic research in occupational asthma has had to struggle with the intractable problem of defining what constitutes a “case,” and how to adequately identify cases in a large population. Our current gold standard, specific bronchoprovocation challenge, though immeasurably valuable for many research purposes, such as deciphering natural history and response to interventions,6,7 suffers both con-

Table 1—Occupational Asthma: What Questions Can Epidemiology Address?

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<th>Etiologic Questions</th>
<th>Questions for Occupational Medicine Practice</th>
<th>Public Health Questions</th>
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<td>1. Identifying causal agent(s)</td>
<td>4. Evaluating diagnostic criteria or strategies</td>
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<td>3. Determining host risk factors</td>
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*From the Yale Occupational and Environmental Medicine Program, Yale University School of Medicine, New Haven, Conn. Reprint requests: Dr. Cullen, 135 College Street, 3rd Floor, New Haven, CT 06510
ceptual and practical limitations. Conceptually, it is the occurrence of bronchospastic responses to exposure within the work environment, not in the laboratory, that is of primary epidemiologic interest. This raises concerns about the correct interpretation of apparently new asthmatic subjects who fail to react in the laboratory, despite clear histories of onset during exposure at work as have occurred with isocyanates. Practically, specific challenge is not a meaningful tool prior to identification of specific agents, such as the elusive cause of potroom asthma, and is not available for use to investigators except at a handful of centers, though this is likely to change.

At the other end of the research armamentarium lies a more serious deficiency of tools for case ascertainment “in the field.” Despite the reliability and content validity of Medical Research Council and American Thoracic Society questionnaires in surveys for many chronic forms of lung disease, including the pneumoniaes, these and modifications of them have proved unreliable and insensitive for asthma. Although the International Union Against Tuberculosis questionnaire correlates better with measures of bronchial reactivity, it remains to be proved a sensitive or specific measure for occupational asthma, nor has a better alternative been adequately tested.

In part because of this problem and in part to replace subjective with objective measures of airway lability at work, increased interest has surfaced in measures of flow at work, either with preshift and postshift spirometry, response to methacholine inhalation, or peak expiratory flow rate (PEFR) records. The latter might have been expected to fulfill the need quite handily, in view of self-administration and good reproducibility once subjects are trained. Unfortunately, the experience with PEFR has been rather disappointing. Compliance, outside of highly motivated patients or clinical research volunteers, is often very difficult to obtain and the results have been very difficult to quantify, resulting in reliance on “expert interpretation” as the best standard, with all the incumbent difficulties.

Though there are undoubtedly other reasons as well, lack of a well-defined end point is likely a contributor to differing perceptions of the incidence of potroom asthma, which has varied from 0% in US studies to 20% in Australia and Scandinavia, with most other estimates lying between 9-22.

Similar problems have frustrated the search for susceptibility or host factors, notably the lack of standard definitions for many of the characteristics sought. Notoriously, atopy has been defined based on history of allergy, variably elicited, or response to skin pricks, variably interpreted. Preexisting airway disease has also been variably classified, ranging from history of symptoms to methacholine or histamine reactivity at hire. Even if these likely important predictors of risk for some causes of occupational asthma (eg, probably potroom asthma, probably not isocyanate asthma) could be classified in a standardized and valid way, there remains the very difficult dilemma of selection biases that always threaten observational research, but are a particular menace in studies of asthma. On the one hand, atopic individuals or those with preexisting airways disorders, are likely to be drawn (or pushed) to jobs with lower levels of irritant and sensitizing exposures. On the other, starting with lower PC20s and more labile airways as a group, workers with these “risks” are more likely to end up being classified as cases by almost any ascertainment strategy short of specific bronchoprovocation, irrespective of any excess risk for actually developing asthma from exposure. As noted earlier, these issues have more than theoretical importance. Much of our ability to limit occupational asthma may hinge on identifying specific, biologically measurable host factors, assuming these can be found.

The last group of problems I want to discuss relates to the circumstances of exposure that cause disease, usually referred to as the dose-response curve. I have already made the point that for asthma, host factors probably outweigh dose factors in terms of importance, ie, an “at-risk” worker is more likely to get asthma in a very well-controlled environment than a “low-risk” worker in a poor one. Nevertheless, the possibility of primary control depends on determining those characteristics that are causal.

Unfortunately, neither the technology for measurement nor our models for classifying exposure are currently adequate to this task. Both for potroom and isocyanate asthma, few data exist to support any interesting theory other than the uninformative finding that within a given workplace, areas of “higher” exposure (ie, more isocyanate vapor or more fluoride, the ubiquitous irritant in potrooms) are associated with more disease. On theoretical grounds, whether these diseases turn out to be caused primarily by sensitization (likely with isocyanates) or by nonimmune injury (likely in the potrooms), it is probable that intermittent peak exposures are more important for pathogenesis than average or total dose levels. Moreover, the form of the agent (eg, vapor vs aerosol), its ability to deposit at a particular level of the respiratory tree, and related issues may turn out to be hugely relevant to risk. Yet neither the methods to measure such patterns in detail, nor effective models for translating such data into classification schemes have been well worked out. Moreover, few investigators have been able to identify study populations that are sufficiently diverse for these characteristics to allow direct risk comparisons.

**What are the Solutions?**

There is a strong proclivity nowadays to look to biomarkers—biological measures of relevant target organ dose, early and mechanistically specific correlates of clinical effect and host susceptibility factors—as the solution when classic epidemiologic strategies falter. Indeed, there are clear roles for this type of approach in the study of occupational asthma, and much progress has already been achieved. For example, clinical investigations of patients with isocyanate asthma have yielded a wealth of insight into the likely immunopathogenesis of this disease. In vitro stimulation tests of blood lymphocytes, following the model that proved successful in the study of chronic beryllium disease, may yield blood tests to differentiate sensitized from nonsensitized individuals. Taking advantage of clinical confirmation by specific bronchoprovocation challenge, preliminary data suggest the possibility that a polymorphism in the major histocompatibility complex recognition sites on antigen-presenting cells may be the basis for host susceptibility, following the example of beryllium sensitization. On the exposure assessment side, efforts to localize the sites of deposition and binding of isocyanates in an animal model using anti-isocyanate antibodies may prove a means for biological...
dose assessment in clinically investigated subjects as well (Meryl Karol, PhD, personal communication, 1995).

But even were these ambitious efforts to be fruitful, many of the methodologic problems would remain. There would still be the need to document that any test of sensitization correlates with occupational asthma in the exposed population, so techniques for recognition of the actual outcome of interest would remain at issue. Measures of exposure would need to be developed to establish that observations from clinical research are relevant by showing differing risk among workers with different pattern of exposure under real conditions. Observations of correlations between asthma risk and a genetic or acquired markers of risk could still be subject to confounding by selection biases, pressuring workers toward or away from exposure. For asthma problems in which the causal agent and mechanism are less well understood, such as potroom asthma, biomarker research is not even a real possibility yet.

Without intending to dampen enthusiasm for the “biological solution,” there is an extraordinary challenge ahead in the further development and refinement of some very traditional tools of our trade. First and foremost, there is no evading the need to develop a reliable, standardized, and practical survey instrument for occupational asthma that can be efficiently used to identify prevalent and incident cases in populations studied cross-sectionally or longitudinally. Ideally this effort should be pursued in a setting in which more definitive confirmatory tests, such as specific challenge, can be done on “positives” and representative “negative” responders. At the same time, the recently rekindled interest in physiologic measures in populations, such as PEFR, must be further explored. Newer automated devices that record data electronically may resolve some compliance and reliability problems, but methods need to be resolved for standardized interpretation. Alternatively, change in methacholine reactivity between exposed and unexposed conditions may prove more consistently predictive of occupational asthma in field studies, but much more experience and more data are needed. Again, the ability to correlate these measures with more traditional approaches such as serial spirometry or response to specific inhalation will be critical.

While technical solutions, such as electronic recording of real-time devices, will ultimately be needed to resolve dose-response relations, even ordinal or qualitative classification schemes comparing groups with different patterns or forms of exposure could be instructive; few such efforts have been published. With few data sets available for empirical confirmation, there has also been little theoretical work on models for evaluating patterns, rather than average or cumulative dose, as predictors of risk.

I shall close with one last thought. Technology, biological and methodologic insight notwithstanding, some of the greatest contributions to our understanding of occupational asthma have come because great observational opportunities were effectively exploited. For instance, the serial observations of Butcher and colleagues29 of a “virgin” workforce at a new toluene diisocyanate plant in Louisiana over 20 years ago has formed the basis of knowledge on which almost all present work relies. Though the technology for air sampling was advanced for its time, and the protocols for screening, nonspecific and specific challenge fairly elegant even by present standards, the most outstanding feature of this landmark study was the willingness to fully utilize an “experiment of nature” for all of its research value. Opportunities to follow well-studied individuals longitudinally through exposures of interest offer the surest prospect for solutions, especially when these can be combined with appropriate testing at baseline and serially as disease emerges, and meticulous and imaginative characterization of the environment. We need to preserve the will and the patience to conduct such painstaking studies, as well as the insight to value them, even in this era of biomarkers.

References
3 Cullen M. Clinical surveillance and management of occupational asthma: tertiary prevention by the primary practitioner. Chest 1990; 98(suppl):196s-201s
Pulmonary Responses to Allergens and Pollutants*

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Indoor allergen exposures are ubiquitous and can lead to significant allergic diseases (including asthma) in significant proportions of the population. Immunologic sensitization and resulting inflammatory conditions on reexposure are responsible for greater susceptibility to other triggers of airway responses. Air pollutants may act as adjuvants, as predisposing exposures producing airway inflammation, and/or as primary agents for airway responses. Different measures of bronchial responsiveness (BR) (including bronchodilator responsiveness and peak expiratory flow [PEF] lability, as well as responses to specific agents or nonspecific bronchoconstrictor drugs) have shown a relationship between these indexes and symptoms, diagnoses, and function, especially asthma.

Finding markers of exposure, and markers of biological responses, are a major feature of the new environmental epidemiology. Immunomarkers are a category of biological markers. The immunologic system (host characteristics) may "cause," mediate, and modulate the respiratory responses to the allergen exposures/doses and likely irritants. Thus, we seek to measure these host characteristics, especially the immunologic factors that modulate the responses to inhaled allergens and irritants, and to find the best markers to measure the exposure dose to allergens.

MATERIALS AND METHODS

The Tucson Health and Environment study, a representative multistage stratified cluster sample, has monitored aeroallergens and irritants indoors and out, with use of time-activity diaries, in over 400 families with children to characterize these exposures. We monitored regional (macro) pollen and mold outdoors using a Burkard 7-day trap sampler (Rickmansworth; Hertfordshire, England) and indoors with a combination of the 7-day Burkard industrial trap and personal monitor. Skin tests for multiple allergens were used to measure specific responses to these allergens; a wheal from the skin test at least 1 mm greater than that resulting from the negative control (diluent) was regarded as positive. Self-reports (American Thoracic Society standard questions) of physician-diagnosed asthma, responses to five screening allergens, and diurnal variation of PEF (our indicator of bronchial lability) were obtained and used to stratify subjects. These were utilized initially as indicators of prevalent pulmonary conditions as well. Individual respiratory responses were monitored with daily symptom diaries and peak flow measurements.

RESULTS

Exposure assessment in Tucson indicated that the proportion of exposure occurring indoors accounts for 50% or more for pollen and 60 to 80% for mold; we assume it is 100% for mites and animal allergens. The distributions of the immunomarkers are related to the distributions of the monitored aeroallergens in Tucson; an example, mesquite, is shown in Figure 1. Among subjects with even minimum (1 mm) skin test responses (ie, minimum immunomarkers), symptoms increase by over 30% with elevated pollen concentrations.

Prevalence rates of asthma, allergy, and BR were related to specific allergen and air pollutant exposures. Using a set of 11 allergens, 56% of subjects had positive immunomarkers of exposure (skin test reactivity). Positive immunomarkers were compared with BR: house dust to which 5.5% re-

Allergy Sx, Meds by Mesquite React.

(Mesquite season only)

![Mesquite Reactivity Graph](http://journal.publications.chestnet.org/pdfffaccess.asgh?url=/data/journals/chest/21729/ on 04/01/2017)

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