Occupational Asthma: What Can it Teach Us?

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Introduction: What is occupational asthma and what causes it?

Occupational asthma was first recognized by Hippocrates in the fourth century B.C., when he described asthma in several different classes of workers. However, it wasn't until the 1920s that the first detailed descriptions of asthma attributable to a specific workplace agent were published. The first reports described asthma in workers exposed to castor bean dust.(9) Over the next couple of decades several other causative agents were described including acacia, vegetable gums, wood dust, metals, and several chemicals.(1) However, it's only been in the last 50 years with the development of specific challenge testing and immunologic testing that the disease has matured as a clinical entity.(14)

We now recognize occupational asthma as the most common occupational lung disease in industrialized nations.(15) It is currently defined as "a disease characterized by variable airflow limitation and/or airway hyerresponsiveness due to causes and conditions attributable to a particular occupational environment and not to stimuli encountered outside the workplace."(1) This is distinctly different from an individual with preexisting asthma whose symptoms worsen at work. The latter is known as work aggravated asthma and has a different pathogenesis and prognosis.(16)

There are two forms of occupational asthma: immunologic and nonimmunologic. Nonimmunologic occupational asthma occurs when an individual is exposed to a high concentration of a respiratory irritant leading to persistent bronchial hyperreactivity and symptoms of intermittent cough and dyspnea. This is also know as reactive airways dysfunction syndrome (RADS) or irritant induced asthma.(17-19) RADS is an uncommon outcome of an irritant exposure. Less than 10% of individuals who suffer an irritant inhalation develop persistent bronchial hyperreactivity.(14, 20, 21) Irritant induced asthma is also the less common form of occupational asthma accounting for only about 15% of occupational asthma in most series.(22-25) In this paper, I will focus exclusively on immunologic occupational asthma (I will refer to this as occupational asthma for the rest of the paper).

Immunologic occupational asthma occurs after a latency period between the onset of exposure and disease. Sensitization to the relevant workplace antigen occurs during this latency period. Disease then occurs in some sensitized individuals if they remain in exposure. The agents that cause occupational asthma are typically divided into two groups, high ($\geq$ 5,000 Daltons) and low (< 5000 Daltons) molecular weight.(26) The majority of the high molecular weight antigens are plant or animal proteins. Reactive chemicals make up the majority of the low molecular weight agents. The low molecular weight agents are not complete antigens but rather act as haptens in the induction of a specific immune response.(26) All of the high and some of the low molecular weight antigens act through IgE mediated mechanisms.(1) IgE has not been documented for the remainder of the low molecular weight chemicals but the pathogenesis of the disease is still immunologic as I will discuss in greater detail below.

The list of agents reported to cause occupational asthma is vast. The most up-to-date list is maintained on the internet (*www.asmanet.com/asmapro/asmawork.htm)* although several published lists of causative agents are also available.(1, 27) In total, over 400 specific agents and

over 140 different industries have been implicated. Some of the more common agents are shown in Table 1.

Table 1: Common agents that cause immunologic occupational asthma

Agent	Industry/activities at risk
High Molecular Weight Agents	
Animal Proteins – rodent urinary antigens, cow dander	Lab animal researchers/technicians, animal handlers, veterinarians, farmers
Latex	Healthcare
Flours and Cereals	Bakers, millers
Insects – storage mites	Bakers, farmers, researchers, entomologists
Molds	Bakers, farmers, logging,
Enzymes – *B subtilis,* alpha amylase, trypsin	Detergent manufacturing, baking, plastic manufacture, pharmaceutical
Low Molecular Weight Agents	
Isocyanates	Painting, foundries (cores), automotive, plastics, polyurethane foams, chemical industry
Anhydrides	Epoxy resins and adhesives, plastics manufacture, polyester resin, chemical industry
Soldering fluxes – colophony	electronics
Wood dust – western red cedar	Woodworkers, furniture manufacture, construction, carpenters
Cleaners/biocides – quaternary ammonium, chloramines T, glutaraldehyde, hexachlorophene	Cleaners, janitors, nurses, endoscopy/OR staff
Metals – platinum, nickel, chromium, cobalt	Welders (stainless steel), foundry workers, machinists, metal workers, aerospace, painters
Drugs – penicillin, cephalosporin, psyllium	Pharmaceutical manufacture, pharmacists, nurses
Acrylates – methacrylate, cyanacrylate	Adhesives industry, crime labs, manicurists, orthopedic surgeons, OR nurses
Persulfate Salts	Hairdressing

Most of these reports describe individual cases or small case series. The majority of what is known about the disease's natural history, pathogenesis and characteristics of the various diagnostic tests comes from studies of only a few agents including western red cedar, colophony, flour, lab animal allergens, latex, enzymes, snow-crab processing, isocyanates, and anhydrides.

Epidemiology: How common is occupational asthma?

From a population perspective there are two different approaches to answer this question. The first is to try to define the incidence or prevalence in the population. Researchers have used a variety of sources to collect this data including both voluntary and mandatory reporting systems and workers compensation claims records. Finland has a mandatory reporting system known as the Finnish Resister on Occupational Diseases (FROD).(28, 29) Great Britain (SWORD), South Africa (SORDSA), France (ONAP), Sweden, Canada (PROPULSE) and the United States (SENSOR) have voluntary reporting systems operational in at least portions of their respective countries.(23, 29-34) The yearly incidences reported vary widely from 1.3/100,000 in South Africa, to 18/100,000 in Finland. France, Great Britain, and the United States reported rates of 3-4/100,000 while the incidence in Quebec, Canada was 6.3/100,000. To put this in perspective, the estimated annual incidence of asthma in Finland is 200/100,000.

However, incidence data from registry sources severely underestimates the actual incidence of disease. In the UK SWORD data there was marked geographic variation in reporting not explained by differences in industry within the regions. This is thought to be due to different reporting rates.(35) In fact, one study suggests the true incidence may be more than double the reported incidence.(36) This likely explains at least some of the difference between the incidence in Finland where reporting is mandatory and the incidence in the voluntary registries described above. Even the estimates from Finland underestimate the true incidence. In Finland, reporting is required via the national worker's compensation system, but self-employed workers don't have to enroll in this system. Disease in the self-employed will thus be underreported. This is especially important as farmers make up a large percentage of the self-employed in Finland and farming is a high risk industry for occupational asthma.(37-41)

Perhaps even more important than underreporting is the problem of a lack of physician recognition of occupational asthma. For example, the United States estimates are derived from the National Institute of Occupational Health's (NIOSH) Sentinel Event Notification System for Occupational Respiratory Disease (SENSOR). Follow-up investigation of only half of the worksites with reported cases of occupational asthma discovered enough additional cases to more than double the initially reported disease incidence.(24, 32) A study by Milton et al. best illustrates the problem of under recognition. In this study, the charts of patients in a large health system that were diagnosed with asthma by their PCP were reviewed. Only 15% of the charts documented an occupational history.(42) Obviously, occupational asthma cannot be diagnosed if the physician doesn't ask about a patient's occupation. In this study, the annual incidence of occupational asthma after the identified cases were reexamined by the investigators was 40/100,000.(42)

In order to avoid the problems of underreporting and lack of recognition many investigators are now approaching the question, how common is occupational asthma, differently. They are now determining the attributable risk of occupational asthma. The attributable risk is the proportion of all cases of asthma that can be attributed to workplace exposures.(43) To date, 24 different studies have directly measured the attributable risk of occupational asthma yielding estimates ranging from 5% to 30%.(37, 44) Three recent meta-analyses have been performed on these, and other studies whose data allowed for the calculation of an attributable risk, and all reached a similar conclusion.(6, 45, 46) The results from the study

by Blanc et al., are shown in figure 1 below. The attributable risk of adult asthma due to one's occupation is between 10-15%

Source of Estimate	Number of Studies	Attributable Risk Estimate	
		Median	Mean
Published estimates	23	9%	12%
Derived from published data	8	25%	26%
Extrapolated from incidence estimates	12	5%	6%
Weighted mean based on study score	28	—	15%
Estimates from reports with highest study scores	12	15%	17%
All studies	43	9%	13%

Figure 1: Cumulative data on the attributable risk of asthma caused by work. Overall, the median is 9%. If only the highest quality studies are considered the median increases to 15%. From Blanc et al.(6)

The attributable risk is even higher if one considers only those patients with new onset adult asthma. In the study by Milton et al., referred to above, the authors performed a prospective cohort study of almost 80,000 adult members of a regional HMO seen over a 3 month period. They then contacted all those patients seen for asthma and conducted further evaluations. They found that of those people that developed asthma de novo, 26% probably had occupational asthma.(42) Likewise, Johnson et al., reexamined the asthmatics identified in the Canadian portion of the European Community Respiratory Health Survey and found that 36% of the cases of de novo asthma were likely related to work.(47)

To put the importance of occupational asthma in perspective, consider the implications of this attributable risk. The prevalence of asthma is 5% and has been increasing over the last 2-3 decades.(48-50) This means that the number of people with occupational asthma could be in the millions in the United States alone. This likely explains the estimated cost of occupational asthma to the United States, 1.6 billion/year.(51, 52) In addition, patients that receive the diagnosis have a higher rate of disability, unemployment, worse symptoms, and poorer quality of life than people with nonoccupational asthma.(53-56) Pursuing prevention of this disease, which is possible (as discussed further below), could thus have a major public health impact.

Occupational Asthma: How to make the diagnosis

There are several published guidelines for the diagnostic evaluation of occupational asthma including a recent web publication from the British Occupational Health Research Foundation (*www.bohrf.org.uk/content/asthma.htm*) .(15, 57) All of the guidelines recommend a stepwise approach to diagnosis. The first step is to suspect the disease. Obviously, patients should have asthma symptoms of intermittent dyspnea, wheezing, and/or cough. However, the history of present illness and the occupational history can provide several important historical clues that should elicit suspicion of an occupational cause (see table 2). Several points deserve further emphasis. As part of the occupational history one should obtain a detailed description of the job tasks, materials used and the surrounding work environment. The temporal association between symptom and exposure onset needs to be determined. This may require detailed descriptions of prior employment to determine if there were common exposures. Exposure to a

known sensitizer, either due to direct use or bystander exposure from coworker use, which precedes the development of asthma symptoms, is suggestive of occupational asthma. Occupational asthma should also be suspected if the patient works in a high risk industry.

Table 2: Historical clues for the presence of occupational asthma

History of Present Illness Clues
New onset asthma
Symptoms worse at work or at night on workdays (or with specific exposures)
Improved symptoms on vacation, over weekends, or other times away from work
Similar symptoms in exposed coworkers
Presence of work-related rhinitis and/or conjunctivitis
Failure to improve with appropriate therapy
Occupational History Clues
Work in a high risk industry (ex. healthcare, lab research, electronics, baking, painting, etc.)
Personal use of a known respiratory sensitizer
Coworker use of a known respiratory sensitizer
High levels of exposure
Presence of Risk Factors
Atopy
Work-related rhinitis
High exposure intensity
Known sensitization to a workplace agent

The history of present illness can provide several important clues as detailed above. At some point in the disease course patients should describe a relationship between symptoms or exacerbations and exposure. However, there are several caveats to this statement. First, some people only develop a late reaction (see below) and thus only develop symptoms many hours after exposure. Therefore, nocturnal asthma that is worse on workdays is suggestive of occupational asthma. In addition, the temporal relationships change with disease severity.(15) As the disease becomes more severe the symptoms become more persistent. Once this occurs, patients may not improve at all even after leaving exposure or improvement may require a more prolonged absence from work before becoming noticeable. In addition, if you are evaluating a patient long after symptom onset they may no longer remember the temporal associations.

The presence of risk factors is also a helpful clue, especially the presence of work-related rhinitis and/or conjunctivitis. Occupational rhinoconjunctivitis frequently coexists with or precedes the onset of occupational asthma.(58-61) Rhinoconjunctivitis more commonly precedes the appearance of occupational asthma if the responsible antigen acts through an IgE mechanism.(16, 60, 62, 63) The presence of occupational rhinoconjuntivitis is also associated with a 5-fold increased risk of subsequent development of occupational asthma especially in the first 2 years post diagnosis.(64)

If the above factors are considered the history is very sensitive for the detection of occupational asthma. Multiple studies have shown a sensitivity of approximately 90%.(65-67)

However, the specificity of the clinical history in these same studies was only about 50%. Therefore, one cannot rely on the history alone to make this diagnosis.(15, 57, 66)

The second step in the evaluation is confirmation of the presence of asthma. Confirmation requires documenting either reversible airflow obstruction or bronchial hyperreactivity.(68) Reversible airflow obstruction can be seen on a single spirometry in the presence of a significant bronchodilator response or over time if there's significant improvement with anti-inflammatory therapy. However, airflow obstruction is not always present in occupational asthma, especially early in the disease or if some time has past since the last exposure.(69) In this case one should perform a methacholine challenge test to document the degree of bronchial hyperreactivity. This test measures the provocative concentration of methacholine inducing a 20% fall in FEV1 (PC20). Asthmatics typically have a PC20 < 4 mg/ml while in normal individuals the PC20 is typically >25 mg/ml.(70) The classic teaching is that a negative methacholine challenge in a worker with ongoing exposure virtually excludes the diagnosis of occupational asthma.(26, 57, 71) However, several reports in isocyanate workers call this dictum into question.(72-74)

Once asthma is established the next step is to objectively confirm a relationship between the disease and the workplace.(15, 57) The gold standard to prove this association is the specific challenge test. In this test the individual is exposed to progressively increasing (but sub-irritant) concentrations of the substance in question. Patients with occupational asthma will have a 20% fall in their FEV1 and/or a 3-fold decrease in the PC20 to methacholine.(1, 15) Unfortunately, this test is only available at a few specialized centers. The other options include documenting immune sensitization to the workplace antigen or documenting worsened pulmonary function during work. The first of these two options is intuitively attractive but suffers from many difficulties. Many of the low molecular weight agents don't act through IgE mediated mechanisms so there are no skin or RAST tests available. In addition, there aren't any standardized reagents for the majority of the antigens that do act via IgE. Variability in the antigen preparations thus limits sensitivity and makes negative tests unreliable. For example, in one recent study of bakers asthma the potency of different commercially available antigen preparations was variable and the sensitivity was compromised only ranging from 45-67%.(75)

For this reason, the preferred approach in most instances remains documentation of work-related decrements in pulmonary function. Simple cross-workshift measurements of spirometry are neither sensitive nor specific and are thus no longer recommended.(76) The most frequently used test is measurement of serial peak flow recordings. The test characteristics are maximized with four measurements per day over at least 2 weeks at work and 2 weeks away from work.(77) The results are then plotted and examined visually for significant drops or excessive

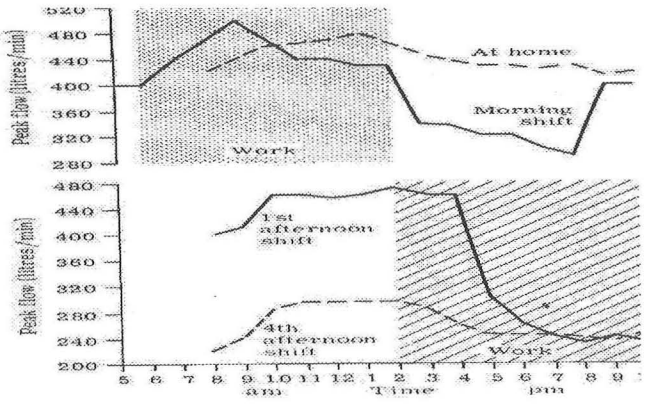

Figure 2: Examples of positive patterns on peak flow recordings.

variability on workdays (see figure 2). Peak flow recordings are limited by patient reliability and compliance with performing and recording the readings.(15) Despite these limitations numerous studies have documented a sensitivity and specificity of peak flow recordings in the range of 85-90%.(15, 65, 77) The other option for documenting a relationship between work and decrements in pulmonary function is to perform serial methacholine challenges both at work and after removal from exposure. The sensitivity of serial methacholine challenges is less than peak flow readings.(65, 71) However, methacholine challenge avoids the problems of patient reliability and compliance so many investigators use it in conjunction with peak flow recordings.(16, 57, 78) Provided the first two steps were followed, documentation of worsened peak flow or increased bronchial hyerresponsiveness during exposure allows for a confident diagnosis of occupational asthma.

Management

The cornerstone of treatment for occupational asthma is removal from exposure. The reasons for this are discussed in the prognosis section below. With removal from exposure approximately one-third of the patients will have complete disease resolution and almost all will stabilize or improve.(1, 14) The pharmacologic management is identical to nonoccupational asthma.(68) Affected workers should also be referred to workers compensation and possibly vocational rehabilitation for training in a new field. Finally, as I will discuss further below, a diagnosis of occupational asthma has public health implications for prevention as there are usually coworkers that either have milder disease more amenable to treatment or remain at risk for the future development of occupational asthma. Disease prevention is one of the many things occupational asthma can teach us about nonoccupational asthma.

Occupational Asthma: What Can it Teach Us?

From a research perspective, occupational asthma offers several unique advantages over the study of asthma in the general population.(79) There is a well defined cohort of people at risk, namely workers exposed to the causative agent.(80) The causative agent is known as is the onset and duration of exposure.(81) In addition, it is possible to directly measure exposure concentrations (i.e. exposure intensity).(14) The natural history of the disease can be delineated as it is possible in many instances to detect the onset of sensitization, pre-clinical or asymptomatic disease(82-84) and the onset of symptomatic disease.(85, 86) Finally, you can remove diseased individuals from exposure. It is thus possible to study each step in the pathogenic chain of events including the development of sensitization, the development of disease, and finally the determinants of persistent disease vs. disease resolution.(86, 87) Unfortunately, occupational asthma does have limitations as a research model for asthma. The population at risk (and with subsequent sensitization and disease) in any given worksite is oftentimes small and limits statistical power. The exposure levels in the workplace are often higher than the antigen levels to which the population of nonoccupational asthmatics is exposed. In addition, much of the population burden of asthma begins in childhood and given the known age-related differences in the immune response it is unclear whether or not studies of occupational asthma will apply to childhood disease.(88) Despite these limitations, the study of occupational asthma has provided many valuable lessons. However, before discussing what

occupational asthma can teach us about adult asthma, I will first need to review what is known about the pathogenesis of nonoccupational asthma.

Asthma Pathogenesis

The old view of asthma pathogenesis centered on reversible airway dysfunction featuring bronchospasm, edema, and mucous hypersecretion.(5) However, over the last 25 years this paradigm has shifted with the recognition of the central role of airway inflammation in the pathogenesis of the disease (see figure 3). In addition, studies of occupational asthma and longitudinal studies of asthmatics now demonstrate that asthma is generally not completely reversible.(1, 89)

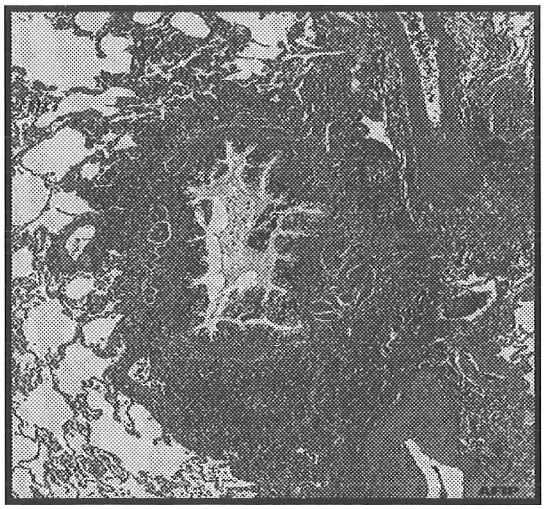

Figure 3: transbronchial biopsy in an asthmatic showing intense airway centered chronic inflammation.

The inflammatory process in asthma begins with the inhalation of antigenic substances. These antigens are taken up and processed by dendritic cells, the primary antigen presenting cell in human airways (see figure 4). The dendritic cells then traffic to the regional lymph nodes.(90) In the lymph nodes, the dendritic cells present the processed antigen via MHC class II molecules on their surface to naïve CD4+ T-cells and B cells.(91) In the presence of IL-4, IL-13, and co stimulatory signals provided through the interaction of CD28 receptors with B7molecules, but the absence of IL-12, T cells whose T cell receptor recognizes the antigen/MHC complex become activated, differentiate and commit to a Th2 phenotype.(92, 93) The activated Th2 type CD4 cells then play a central role in the initiation and perpetuation of airway inflammation.(94, 95) They secrete a group of cytokines including IL-4, IL-13, and IL-5(5, 7, 90, 96, 97) (the Th2 cytokines) that have a variety of effects including enhancing B cell switching to IgE production and eosinophil recruitment and activation.(96) The IgE binds to high affinity IgE receptors (FcεRI) on the surface of mast cells and basophils.

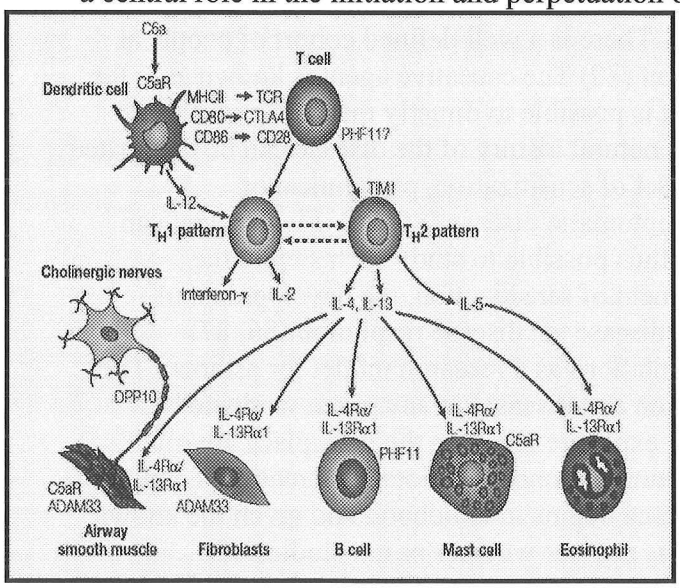

Figure 4: Schematic of asthma pathogenesis with involved cells, cytokines and proposed genetic components, from Wills-Karp, et al.(7)

Subsequent re-exposure to antigen then causes an inflammatory response. This response occurs in two potential phases (see figure 5, next page). The first phase is known as the early phase reaction. It occurs after antigen binds to IgE on the surface of mast cells and basophils. Antigen binding induces cross-linking of IgE which initiates an intracellular signaling cascade culminating in the release of preformed mediators including histamine,

tryptase, chymase, eicosanoids, free radicals and pre-formed Th2 like cytokines.(5, 90) These mediators induce acute bronchoconstriction, mucous secretion, and increase microvascular permeability leading to airway wall edema. The end-result clinically is the appearance of symptoms of dyspnea, cough, and wheezing within minutes of exposure. If the individual leaves exposure, these symptoms resolve within hours.

However, the antigen also activates memory T-cells. These T-cells secrete mediators that work in concert with the preformed mediators released above to recruit inflammatory cells into the airway. These cells include eosinophils, further memory CD4 Th2 cells, macrophages, basophils and neutrophils.(5) The origin of the recruited cells appears to be the circulation and the bone marrow.(98-100) Of these, the eosinophil is probably the most important effector cell and it is also activated by the same group of mediators. The activated eosinophils release a variety of mediators which function to further the build-up of activated inflammatory cells within the airway. In addition, the substances released by the eosinophils (and other effector cells) cause direct tissue injury of the airway epithelium probably via the production of large amounts of free radicals.(101) The injured epithelium is then an important contributor to the inflammatory process and subsequent events.(91) The sum total of these events is known as the late phase reaction. Clinically, patients develop asthma symptoms beginning six to nine hours after allergen exposure and lasting for days. Increased bronchial hyperresponsiveness may last for weeks.(69, 102)

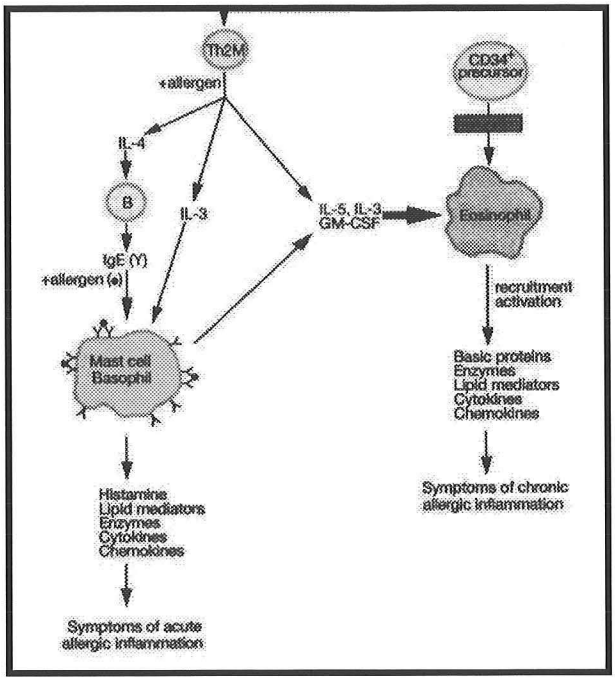

Figure 5: Illustration of allergic inflammation demonstrating the central role of the memory T cell (Th2M) and the cell types and mediators in early vs. late allergic inflammation. From Holt, et al.(4)

With acute exposure to antigen, sensitized asthmatics develop one or both of the above responses. In some, only the early response occurs while in others it's only the late response. This is known as an isolated early or late response. If both responses occur it's known as a dual response.(1) In the setting of ongoing antigen exposure the inflammation that began with the late phase reaction becomes chronic (see figure 3 above).

Chronic inflammation in the airways has been widely demonstrated in all forms of asthma.(1, 5, 103, 104) Classically, asthma has been broadly classified clinically as extrinsic (atopic) or intrinsic (non-atopic). Extrinsic asthma features documented IgE mediated sensitivity to common inhaled allergen documented by an immediate response on skin prick testing or positive blood IgE RAST testing. This is identical to occupational asthma induced by high molecular weight agents.(81) In intrinsic asthma IgE sensitivity can't be documented, which is similar to what's seen in occupational asthma induced by many of the low molecular weight antigens. In the past, there was some debate over whether or not intrinsic asthma shared the

same immunologic pathogenesis as extrinsic. However, lessons from occupational asthma and some more recent data provide overwhelming evidence of the immunologic nature of both forms of asthma. Low molecular weight antigens that don't elicit an IgE response still act through an immunologic mechanism.(14) Occupational asthma secondary to these agents only develops after a latency period during which sensitization occurs.(1) An immune response can be demonstrated by lymphocyte proliferation assays when T cells from sensitized individuals are cultured in the presence of antigen.(105-107) In addition, symptoms are elicited in laboratory challenges to miniscule doses and the sensitivity persists even years after removal from exposure as one would expect with allergen induced disease.(108) Moreover animal, and more recently human, data show that IgE is not required for the development of the asthmatic phenotype. IgE knockout mice and B-cell deficient mice still develop allergic airway inflammation but mice deficient in MHC class II molecules do not.(109, 110 , 111) In addition, sensitization can be transferred by injection of lymphocytes from sensitized mice into naïve mice.(112, 113) IgE independence has also been demonstrated in humans. Cat allergic patients exposed to peptide fragments of Fel d 1 (the major cat antigen) develop IgE independent late asthmatic reactions.(114) Most importantly, the pathologic changes in the airway including chronic eosinophilic inflammation are identical in all forms of asthma.(10, 103, 115-117)

The ongoing cycle of chronic inflammation with injury to the airway wall and epithelium leads to an abnormal repair process known as airway wall remodeling. The components of remodeling include increased wall thickness, subepithelial fibrosis in the lamina reticularis (the layer just below the true basement membrane), myofibroblast hyperplasia, myocyte hypertrophy and hyperplasia, mucous gland hypertrophy, and increased density of blood vessels (see figure 6).(94, 118-120)

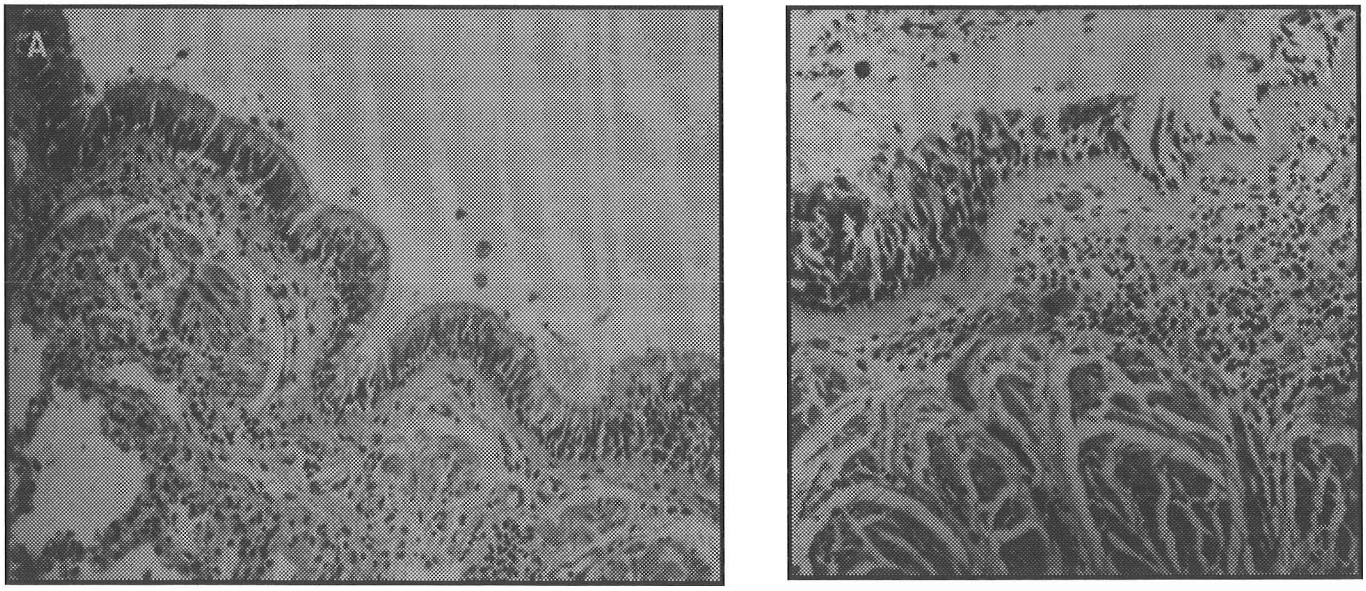

Figure 6: A – normal airway wall. B – airway wall in severe asthma demonstrating epithelial sloughing from injury, inflammatory cell influx, subepithelial fibrosis, and smooth muscle hypertrophy and hyperplasia, from Bousquet et al.(5)

The overall thickness of the airway wall can be two to three times normal and the myocyte mass is more than doubled.(120) The end result is a narrowed airway prone to mucous plugging and excessive constriction with smooth muscle contraction. The long term consequences of airway remodeling are still not completely understood. However, airway wall remodeling is correlated with disease severity and the decline in FEV1.(94, 121, 122) In addition, studies consistently demonstrate a relationship between remodeling and bronchial hyperreactivity, the physiologic hallmark of asthma.(122-124) The natural history of remodeling is still not understood but many authors hypothesize that the accelerated decline of FEV1 seen in asthma is a result of airway wall remodeling and that this may be permanent.(5, 90, 94, 118-120, 125)

Insights from Occupational Asthma

Although our understanding of asthma pathogenesis has increased markedly over the last decade, many questions still remain, especially at either end of the process. What determines who develops sensitization and disease? We know that both genetic and environmental factors play a role (see below); however, the actual genes and exposure characteristics remain unclear. What are the determinants of prognosis? Is remodeling permanent? Occupational asthma is uniquely suited to study these questions because we can define the time of exposure onset and cessation, measure exposure levels and characteristics, and detect the onset of sensitization and disease. In other words, occupational asthma allows study of the environmental and genetic determinants of sensitization and disease and how they interact. In addition, it allows study of the prognostic factors independent of the environment as the individual can be removed from exposure to the causative antigen.

The Role of the Environment

The environment clearly plays a role in asthma pathogenesis. Studies of identical twins show that disease concordance is not 100% as would be expected from a purely genetic disease.(126, 127) More importantly, the incidence of asthma has been increasing over the last 20 years and this cannot be explained on the basis of genetics alone.(48, 128-131) Studies estimate that up to 50% of asthma is environmentally determined.(97, 130) However, the specific environmental factors remain obscure.(7) Environmental factors of potential importance include: exposure dose, exposure route, characteristics of the antigen itself, and coexposure to respiratory irritants.

The Effects of Exposure Dose

Exposure dose is the best researched exposure factor. Early efforts at demonstrating a dose-response relationship in occupational asthma met with several difficulties. Up until the early 1990s we weren't able to measure the airborne exposure levels for most high molecular weight antigens. As a result researchers substituted crude exposure measures like hours worked or job category.(132, 133) Many studies only looked at symptoms and we now know that in any given workforce there are many symptomatic employees without sensitization.(56, 63, 134-136) For example, in a prospective cohort study of 300 bakers only half of the individuals with chest symptoms had specific sensitization to flour antigen.(135) The cause of the symptoms in

individuals without evidence for a specific immune response is unclear but at least one study suggests coexposure to respiratory irritants like endotoxin.(137) In addition, a large proportion of sensitized workers do not have symptoms,(12, 136, 138-141) although they are at a markedly increased risk for subsequent symptom development.(55, 136, 138, 142) These factors can obscure the dose-response between exposure and the specific immune response when the outcome measured is symptoms alone.

Finally, the early studies were cross-sectional and didn't address the healthy worker effect. The healthy worker effect is a form of survival bias in which workers who develop symptomatic allergies leave the workforce.(1) Monso, et al. confirmed that the healthy worker effect does occur in high risk industries like animal health technology, healthcare, and baking.(143) In order to compensate for the healthy worker effect, one must examine a workforce during the time that most of the sensitization occurs.

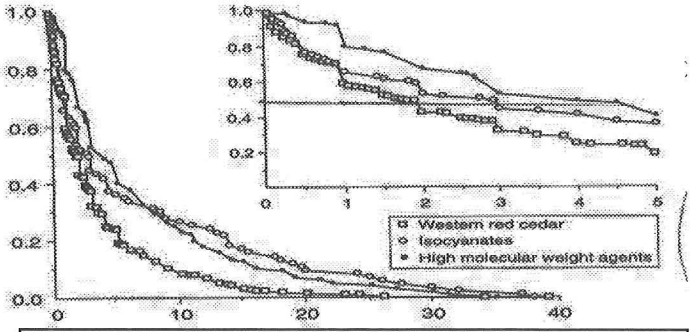

Figure 7: Graphic illustration of the time course for the onset of sensitization. From Bernstein, et al. (1)

As shown in figure 7, the majority of incident sensitization occurs during the first 4-5 years of exposure.(1, 144) For example, in a study of laboratory animal workers the authors could not demonstrate a dose response for the entire workforce. However, when the analysis was restricted to workers with less than four years of employment a clear dose response relationship was seen with a 7 fold higher risk of disease in those with the highest exposure.(134)

Over the last 10 years numerous studies have been performed that controlled for the above factors. The results now provide clear and convincing evidence for the presence of a dose response for sensitization with a direct relationship between sensitization rates and exposure dose.(3, 43, 104) Many of these studies are prospective studies of trainees initially surveyed prior to exposure onset.(12, 135, 144-146) Others are cross-sectional but use personal exposure monitoring and control for bias like the healthy worker effect.(8, 13, 138-141, 147, 148) In total, these studies demonstrate a clear effect of increasing exposure dose on the development of sensitization. For example, in a study by Meredith et al. each 0.1 ppb increase in airborne isocyanate levels led to an 8% increase in the risk for developing isocyanate asthma.(148) Other representative data are shown in figure 8. Figure 8a shows data from a prospective cohort study

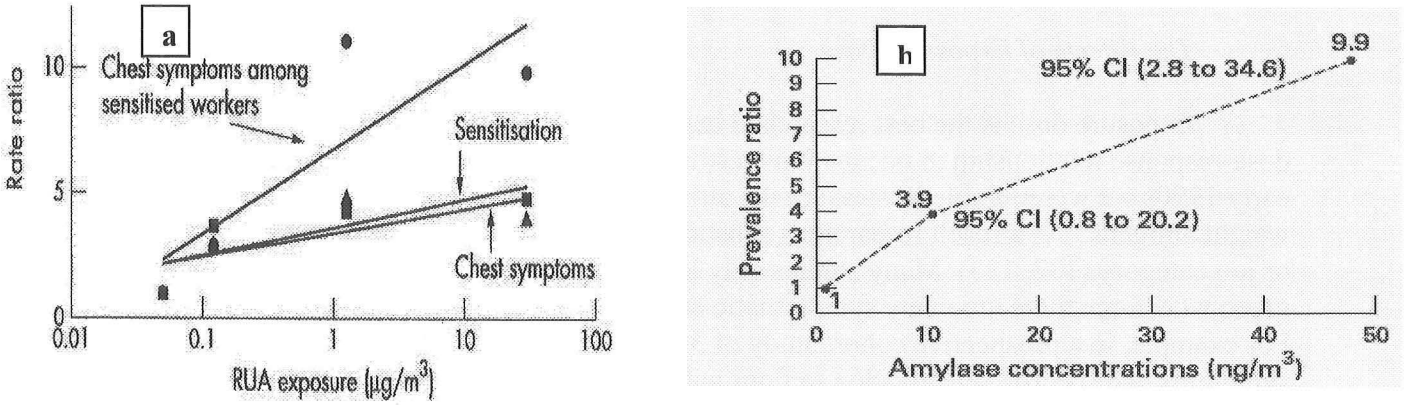

Figure 8: a – show effect of increasing exposure to rat urinary antigen on incidence of sensitization and on the development of symptoms in those already sensitized. From Nieuwenhuijsen(12) b – shows effect of increasing exposure to α–amylase on the prevalence of sensitization. From Nieuwenhuijsen(13)

of 342 laboratory animal workers. The relative risk of sensitization increases steadily up to a relative risk of 5 as one progresses from the lowest to the highest exposure quartile.(12) Figure 8b shows data from a cross sectional study of 495 bakery employees. The prevalence of disease was almost 10 fold higher in workers with the highest exposure.(13) Similar results have been reported across a wide variety of industries and with a wide variety of protein and chemical antigens including latex, animal proteins, enzymes, flour, anhydrides and isocyanates. (8, 12, 13, 135, 138-141, 144-148)

Increasing the exposure dose not only increases the risk of sensitization but it also increases the risk of disease in those already sensitized.(12, 141) As shown in figure 8a, the risk of developing symptoms in rat sensitized workers increases as exposure to rat urinary antigen increases. The sensitized workers in the highest exposure category had a 10 fold higher risk of developing asthma symptoms. The slope of the dose response for symptom development in sensitized laboratory workers is even greater than the slope for the initial development of sensitization. Houba et al. found similar results in a study of bakery workers exposed to wheat antigen. In that study, over 50% of the sensitized workers in the high exposure category developed allergic symptoms.(141)

Thus, in occupational asthma, exposure dose is a very powerful determinant of sensitization and disease. In fact many studies show that a high exposure dose is the strongest risk factor for development of occupational asthma.(3, 13, 135, 139, 147, 148) However, the effect of dose on the incidence of sensitization varies with the genetic susceptibility of the individual. For example, Houba et al. studied a cohort of 178 bakery workers (figure 9). The prevalence of sensitization increased steadily in the entire cohort up to 30% in the high exposure category. However, when stratified by atopy it's clear that all of the sensitization at the lower exposure levels occurred in atopic workers. Non-atopic workers only developed sensitization at the highest exposures. The prevalence of sensitization in non-atopic workers in the highest exposure category was markedly less than in atopic workers (8% vs. 55%).(8) Several other studies also show that atopic individuals are at increased risk for sensitization at all exposure doses but particularly at the lower exposure levels.(134, 135, 141, 145)

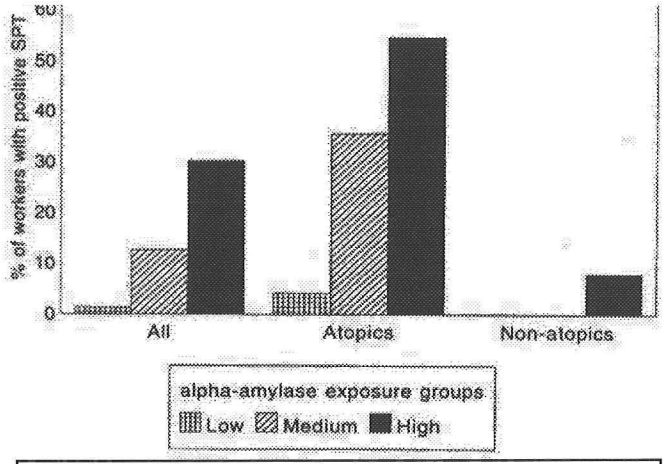

Figure 9: How atopy interacts with exposure dose to influence risk. From Houba et al.(8)

The clear effect of exposure dose on disease risk raises the possibility that a threshold exposure exists below which sensitization does not occur. This has been investigated by a number of authors and the preliminary data suggests that such a threshold does exist. For example, Baur et al. measured airborne latex antigen levels in 32 areas of several hospitals. They examined the employees working within theses areas for evidence of sensitization as defined by a positive latex-specific IgE on RAST testing. They found that sensitization did not occur in areas where airborne latex allergen levels were below 0.6 ng/m^3(figure 10).(149) Similarly, Grammer et al. performed a prospective cohort study of 286 workers at a trimellitic anhydride (TMA) manufacturing facility. Immune sensitization did not occur in areas where the airborne exposures to TMA were maintained below 0.002 mg/m^3.(146) Several other authors have published evidence for a threshold dose for a variety of other protein and chemical antigens.(3, 146, 150, 151) However, the threshold exposure concentration varies widely between studies of different exposures and suggests a different threshold may exist for each antigen.

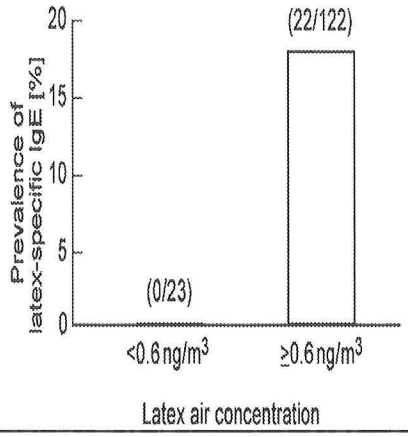

Figure 10: Threshold dose for latex sensitization. From Baur, et al.(3)

Implications for Prevention

The presence of a dose response between the level of airborne exposure and the development of disease and especially the potential for a threshold exposure dose has major implications for prevention. Reducing the level of airborne antigen should lead to a reduced incidence or possibly even complete prevention of occupational asthma. This theory has been put into practice with success at the level of individual institutions and entire industries. Fisher, et al. studied the effects of several programmatic changes designed to reduce the exposure to laboratory animal antigen at a pharmaceutical company research institute. They found a marked reduction in the incidence of laboratory animal allergy in the two years after the changes.(152) Similar results were seen at a teaching hospital and a dental school after changing their latex gloves from high protein powdered gloves to low protein powder-free gloves.(153, 154) In the dental school study there was a 70% fall in the incidence of latex sensitization after the change.(153) In Germany, the government changed the regulations for hospitals requiring a shift to powder-free latex gloves. As shown in figure 11, the number of cases reported to the workers compensation companies fell drastically after the change to powder-free gloves.(11) The

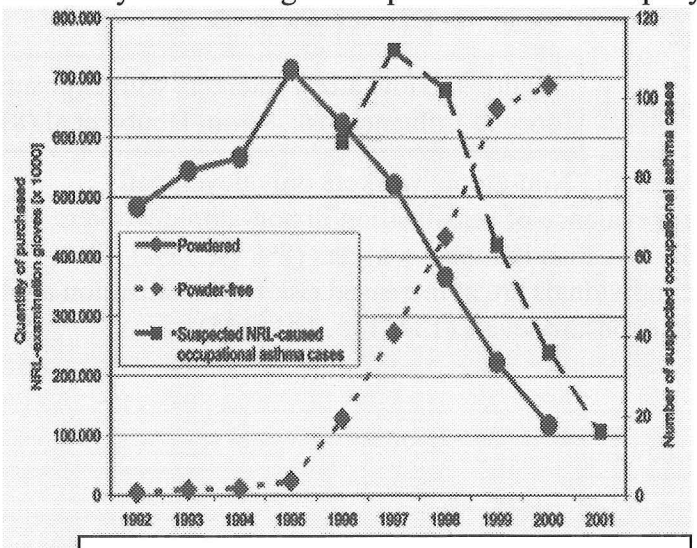

Figure 11: The number of latex allergy cases falls in concert with reduced powdered latex glove use. From Allmers, et al.(11)

best example of the potential for exposure reduction to prevent disease comes from the detergent industry. In the late 1960s bacterial enzymes were added to detergents. Soon thereafter an outbreak of disease was reported with sensitization developing in about half the workforce and occupational asthma appearing in almost 20% of exposed workers.(155, 156) The industry then altered work practices and encapsulated the enzymes resulting in a marked reduction in exposure levels. The end result was a near total elimination of occupational asthma in enzyme workers.(157, 158) The importance of the exposure controls was recently illustrated when they were ignored at a modern plant resulting in a disease outbreak of the same magnitude as the initial reports.(159)

Other Exposure Factors

There has not been nearly as much research into other exposure related factors. Two areas with some interesting research deserve further comment, exposure route and the effect of coexposure to irritants. The above discussion illustrates the importance of airborne exposures. However, what about other exposure routes like the skin? This question was fueled by two clinical observations. The risk of developing isocyanate asthma is increased in workers with known dermal exposure (skin staining) (see figure 12).(160-162) In addition, the incidence of occupational asthma is lower in workers sensitized to lab animals than in workers sensitized to latex where skin sensitization is more common.(136, 144)

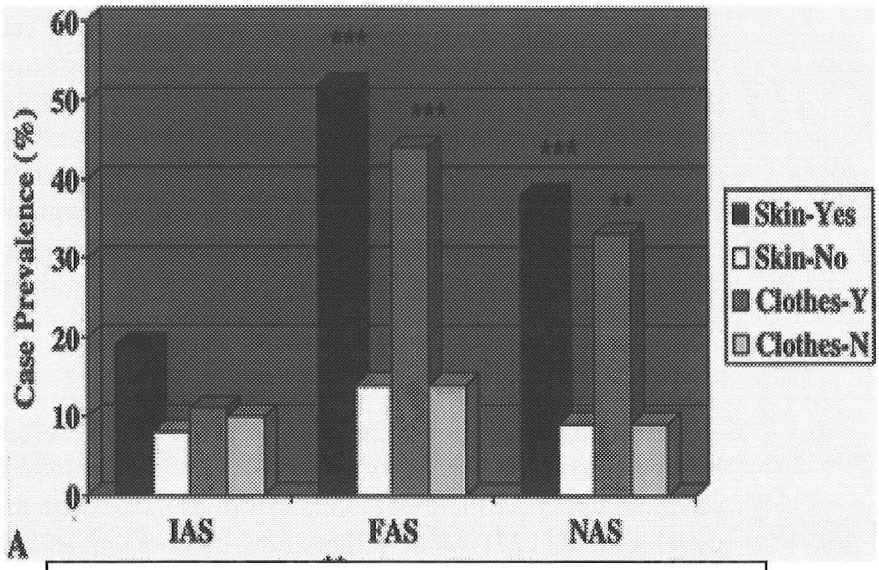

Figure 12: Effect of skin exposure on isocyanate induced asthma. There is a significant increase in asthma with skin or clothing staining. From Petsonk, et al.(2)

There are now a number of animal studies using a variety of isocyanates and anhydrides supporting the concept that skin sensitization can play a role in respiratory disease.(163-166) In these studies animals are repeatedly exposed to topical applications of the chemical inducing immune sensitization. They are then exposed to airborne chemical for the first time and develop typical asthmatic reactions with bronchoconstriction, increased airway hyperreactivity, and influx of eosinophils and activated Th2 CD4 T-cells into the airway. Skin involvement is also potentially important with regards to prevention. Dearman et al., have shown that the immune response of mice to skin sensitization can be used to define which chemicals are potential respiratory sensitizers. They've shown that known chemical asthmagens like isocyanates, anhydrides, and platinum salts induce a Th2 type cytokine response in regional lymph nodes after repeated skin exposure. This is in contrast to chemicals that cause contact dermatitis which cause a Th1 type cytokine response in regional

lymph nodes.(167) If confirmed, this assay may be useful when developing new chemicals for use in industry.

The role of coexposure to irritants is even less certain. There isn't any occupational asthma data in this regard as of yet. However, there are some interesting animal models. Mice exposed to either cigarette smoke or diesel fumes do not develop allergic reactions to either substance. However, if one exposes mice strains that don't typically develop allergy (C57BL/6) to ovalbumin and either diesel or cigarette smoke they develop allergic reactions with elevated IgE to ovalbumin and typical asthma pathology in airway walls.(168, 169) Mouse strains that do develop IgE responses (BALB/c) to ovalbumin develop a much more intense inflammatory reaction with coexposure to diesel or cigarette smoke.(168, 169) If these results could be extended to humans the implications would be tremendous, both in the workplace where coexposure to irritants is common and in the general population because of the irritant effects of many air pollutants including ozone.

In summary, research into the determinants of sensitization and disease in occupational asthma clearly demonstrate that exposure dose is extremely important and that it is possible to prevent asthma in exposed workforces by reducing exposures. The data also suggests that alternative exposure routes (e.g. dermal exposure) and coexposure to irritants may play a role in development of disease. These same tenets almost certainly apply to nonoccupational asthma. However, the exposure data also indicate a significant interaction of genetic susceptibility with exposure dose. This interaction is probably of even greater importance in nonoccupational asthma where the level of exposure to antigen is almost certainly lower.

The Genetics of Asthma

It has been known for decades that asthma clusters in families and that a positive family history is a risk factor for asthma.(90) In addition, twin studies show higher concordance rates in identical than non-identical twins. Both of these facts indicate that genetics play a role in asthma development.(127) Most authors now believe that asthma occurs when relevant exposures occur in genetically susceptible people.(127, 130) The data from occupational asthma discussed above certainly supports this theory. The methods used to study asthma genetics thus far include association studies in candidate genes in which the distribution of polymorphisms within a candidate gene is compared in patients with a given phenotype versus controls.(7) The second study method is a genome wide screen looking for linkage between phenotype and chromosomal regions.(7) These studies show that asthma is a complex genetic disease in which multiple genes are involved rather than a single dominant gene.(170-172) However, determining which genes are involved has been difficult for a variety of reasons.(97, 173, 174) As with all genetic studies, one must overcome the problems of confounding and linkage disequilibrium.(14) The polygenic nature of the disease also causes difficulties because in different individuals different patterns of polymorphisms may lead to the same phenotype. Genetic studies of asthma are also hampered by incomplete penetrance and epistasis (the interaction of polymorphisms is different from the addition of their individual effects). Finally, there is the problem of a high phenocopy rate. Phenocopy occurs when a strong environmental stimulus causes disease in individuals without genetic susceptibility.(173, 175)

Despite these difficulties 16 genome wide-screens in 12 different populations have been completed.(7, 170, 176, 177) In total, 20 separate chromosomal regions encompassing nearly half the genome have been linked to asthma.(127, 173) However, only 8 regions have been consistently linked to asthma (see table 3).

Table 3: Chromosomal regions with consistent linkage to asthma and related phenotypes and their proposed candidate genes

Chromosome Region	Candidate genes
2p	Cytotoxic T-lymphocyte-associated protein 4 (CTLA4)
5q23-33	IL-3, IL-4, IL-5, IL-9, IL-13, CD14, β-adrenergic receptor
6p21.1-p23	HLA, TNFα,
7p	unknown
11q13-21	Glutathione-s-transferase, high affinity IgE receptor (FcεRI)
12q21-24	Stem cell factor, interferon γ, STAT6, leukotriene A4 hydrolase (LTA4H), NOS1
13q12-14	unknown
20p13	ADAM33

Of these the candidate genes on chromosome 5, 6, and 11 have received the most attention. Unfortunately, it has been difficult to obtain reproducible results when examining the known candidate genes in these regions with the possible exception of two recently discovered genes; ADAM33 and Chitinase.(178, 179) Some of the difficulty is likely related to the many varied phenotypes in asthma. A precise phenotype is essential for any genetic study. One author concluded "a clear cut definition might be the most essential basis for any genetic study."(173) Unfortunately, establishing a precise phenotype definition in nonoccupational asthma has proved difficult. As a result, many studies have used easier to define intermediate phenotypes like bronchial hyperreactivity, skin test positivity (i.e. atopy), or elevated total IgE. The assumption in studies using intermediate phenotypes is that the genes involved will be important to asthma as well. Although this is a rational approach the above assumption may not always prove true. For example, studies in occupational asthma consistently demonstrate that only a minority of sensitized individuals develop asthma.*(12, 13, 60, 106, 134-136, 141, 180, 181)* Thus, it is quite possible that some of the genes involved in atopy are not involved or may even be protective with regards to asthma.

Occupational asthma is well suited for the study of asthma genetics because it is possible to define the phenotype with much greater precision than in nonoccupational asthma. In addition, the control group is more clearly at risk than in studies of nonoccupational asthma. Occupational asthma is not a good model for linkage studies but it is an excellent model for testing candidate gene hypotheses and several candidate gene association studies have been performed in occupational asthma.(81, 172)

The majority of candidate gene studies in occupational asthma have focused on HLA associations. The promising new genes noted above have not yet been examined in occupational asthma. Unlike nonoccupational asthma where it has been difficult to find significant HLA associations, several positive associations have been reported. However, with the exception of

the associations in isocyanate asthma, most of these studies have not yet been reproduced in different populations so the results should be considered preliminary. The results are summarized in Table 4.

Table 4: HLA associations in Occupational Asthma

Causative Antigen	HLA Risk Factor	HLA Protective Factor
IgE Mediated		
Rat Urinary Antigen(182)	DRβ1*07	DRβ1*03
Platinum Salts(183)	DRβ1*03	DRβ1*06
Soybean Epidemic Asthma(184)	DRβ1*13	-
Latex (Hev b1)(185)	DRβ1*0401	-
Anhydrides Group 1 (PA, TMA, TCPA)(186)	DRβ1*03 (only TMA, TCPA)	-
Anhydrides Group 2 (HHPA, MHHPA, MTHPA)(187)	DQβ1*0501	-
Non-IgE Mediated		
Western Red Cedar (plicatic acid)(188)	DQβ1*0603, DQβ1*0302	DQβ1*0501
Isocyanates(189-191)	DQβ1*0503	DQβ1*0501

At first glance it appears there aren't any consistent associations. However, another explanation is that the HLA association varies with the causative antigen. For example, the different anhydride groups noted above have very different chemical structures and are known to induce antibody responses with little or no cross-reactivity, indicating a different antigen structure.(192) It is thus quite conceivable that antigens of different structure would have different binding affinities for HLA molecules thus explaining the varied associations seen above.

If the binding affinity is the key then it should be possible to detect amino acid substitutions that could potentially affect antigen binding. For example, rat urinary antigen is a lipocalcin protein which functions as a carrier to transport hydrophobic ligands. In the study by Jeal, et al. on 741 employees of various pharmaceutical companies, patients with occupational asthma secondary to rat exposure were 4 times more likely to carry the DRβ1*07 allele.(182) Analysis of the HLA associations revealed that the susceptibility allele, DRβ1*07, was the only frequent DRβ1 polymorphism in the exposed population whose binding pocket was hydrophobic. DRβ1*07 has 3 unique amino acids. One of these, the hydrophobic amino acid leucine, is located on the floor of the peptide binding groove and is a peptide contact residue.

DRβ1*03, the protective allele, had the most hydrophilic binding pocket with a hydrophilic arginine at position 74 on the α helix, a peptide contact residue.(182) In addition these two DRB isomers differ from each other at 7 positions, 6 of which are hydrophobic in DRβ1*07. It is quite conceivable that rat urinary antigen, with its known binding affinity for hydrophobic molecules, is more likely to bind to the hydrophobic DRβ1*07, and not the hydrophilic DRβ1*03, thus explaining the above associations. In the case of isocyanates, the susceptibility allele, DQβ1*0503, differs from the protective allele, DQβ1*0501, only at position 57 with an aspartic acid in DQβ1*0503 and a valine in DQβ1*0501.(191) A functional role for this amino acid substitution was suggested by analyzing all 15 DQβ1 isomers for the presence of an aspartic acid at position 57 ($DQ\beta1Asp^{57+}$). Homozygotes for any $DQ\beta1Asp^{57+}$ isomers had a 6 fold higher risk of isocyanate-induced asthma.(189, 191) Finally in the latex Hev b 1 antigen study noted above, the Hev b 1 was broken down into peptide fragments and the peptides were cultured with T cells from sensitized individuals and non-sensitized but exposed controls. They were thus able to determine the specific peptide epitopes within the molecule that functioned as antigen and induced T cell proliferation in sensitized individuals. They also showed that the proliferative response were restricted to the DRβ1*0401 isomer.(185) This result was not surprising as validated computer modeling of the antigen predicted that DRβ1*0401 was the primary HLA isomer with binding affinity for the Hev b 1 peptide epitopes.(185, 193)

The above data suggests that HLA associations are important in asthma and that they are likely functional in nature (i.e. not from linkage disequilibrium or confounding).(194) This may also explain the consistent association seen on genome screens with chromosome 6p21.1-p23. The data also illustrate two other points that need consideration when conducting HLA association research. First, high resolution typing is critical. The DQβ1*0503 association for isocyanates could have been canceled out by the protection offered by DQβ1*0501 if only low resolution typing had been performed. Second, HLA associations are a great example of gene-environment interactions. In the case of HLA polymorphisms, genetic susceptibility varies with exposure.

The interaction between atopy and exposure dose discussed above also illustrates the importance of gene-environment interactions in asthma. However, to date there have been very few attempts to examine interactions between specific genes and the environment in occupational asthma. The study on HLA polymorphisms in workers exposed to platinum salts by Newman Taylor et al. merits further discussion in this regard.(183) In that study the HLA polymorphism was a much greater risk factor in the patients with lower exposure levels. If confirmed, this could have important implications for nonoccupational asthma where it is likely that the exposure levels are lower.

A person's genetic background may not only influence the development of disease but could also influence the prognosis. This is one reason for the importance of a clear phenotype definition when studying asthma. For example, if a gene is primarily associated with a poor prognosis a study of severe asthmatics would likely show an association while a similar study in patients with mild disease might not. Occupational asthma is an ideal model to try and separate this as the environmental factor driving the disease can be removed. To date no study has specifically examined this question but studies in one asthma candidate gene, glutathione-S-transferase, are of interest in this regard.

As noted above, oxidant related epithelial injury is an important factor in the pathogenesis of the disease. It follows that one's anti-oxidant defenses are important as well. Glutathione-S-transferase (GST) is one of the body's most important anti-oxidant defenses and polymorphisms in the gene are know to affect function.(195) These factors make GST a likely candidate gene. Researchers have focused their attention on the pi class gene (GSTP1) because it accounts for 90% of the cytosolic GST in human airway epithelium and it is located in the 11q13-21 chromosomal region consistently associated with asthma in genome screens.(196) Some studies in nonoccupational asthma suggest a protective effect from the Val^{105} GSTP1 isomer.(197, 198) Studies in occupational asthma do not confirm an association between the GSTP1 isomers and the development of asthma.(199, 200) However, in isocyanate workers there was an association between the GSTP1 isomers and disease severity. Individuals homozygous for the Val^{105} GSTP1 isomer were less likely to have severe bronchial hyperresponsiveness.(199) These results suggest that glutathione-S-transferase polymorphisms may have a greater role in determining prognosis than susceptibility.(79)

Occupational Asthma and Prognosis

Studies in occupational asthma provided some of the first evidence that asthma is not a completely reversible disease. A series of studies in the late 1970s and early 1980s followed patients after they were removed from exposure. These studies found that in the majority of cases asthma persisted for years after the inciting stimulus was removed. These studies covered a variety of antigens including red cedar, colophony, snow-crab, and isocyanates and showed persistent disease in 30-80% of patients despite removal from exposure.(201-206) This is not to say that removal from exposure isn't important.(1, 207) Studies also showed that the majority of people who leave exposure have improvement in their symptoms and bronchial hyperresponsiveness.(201, 202, 206, 208) On the other hand, the outcome of people who remain in exposure is worse. Most people who remain in exposure do not improve or demonstrate disease progression.(201, 202, 206, 208, 209) In addition, fatalities have been reported in patients not removed from exposure.(210-212)

Even with removal the time course for improvement is slow. Natural history studies in snow crab processing workers with occupational asthma show that it takes a year for FEV1 to plateau and even longer for bronchial hyperresponsiveness.(213) More recent studies on patients with occupational asthma from a variety of exposures confirm that bronchial hyperresponsiveness improves the most in the first 2.5 years but demonstrate that continued, although slower, improvement continues for many years thereafter.(214, 215)

Several clinical factors have been associated with outcome. A longer duration of exposure before symptom onset, a longer duration of symptoms prior to diagnosis, and greater disease severity defined either by the degree of bronchial reactivity or FEV1 are all associated with worse prognosis.(25, 201, 216, 217) All of these factors illustrate the importance of early diagnosis and treatment. As noted above, the primary treatment of occupational asthma is complete removal from exposure. Unfortunately, this is not feasible in nonoccupational asthma. However, there is some preliminary data indicating a benefit from reduction of exposure and from treatment with inhaled corticosteroids in the face of ongoing exposure. Trimellitic

anhydride workers with occupational asthma who were moved to lower exposure jobs showed significant declines in the level of specific IgE and most also showed reduced symptoms.(218) Recent studies of occupational asthma from various causes showed that treatment with inhaled corticosteroids was associated with disease stabilization even with continuous exposure.(219, 220) In addition, other studies show that the best results are achieved if treatment with inhaled corticosteroids is initiated quickly.(221) In aggregate, these studies support the importance of early diagnosis followed by early interventions on exposure and early anti-inflammatory treatment in adult asthma.

The mechanism behind disease persistence even after exposure removal remains unclear. One theory related to remodeling inducing permanent scarring in the airway wall. However, the data don't support this as the collagen deposition in the lamina reticularis resolves after removal from exposure (see figure 13).(10, 115) However, the inflammation persists. Both studies noted

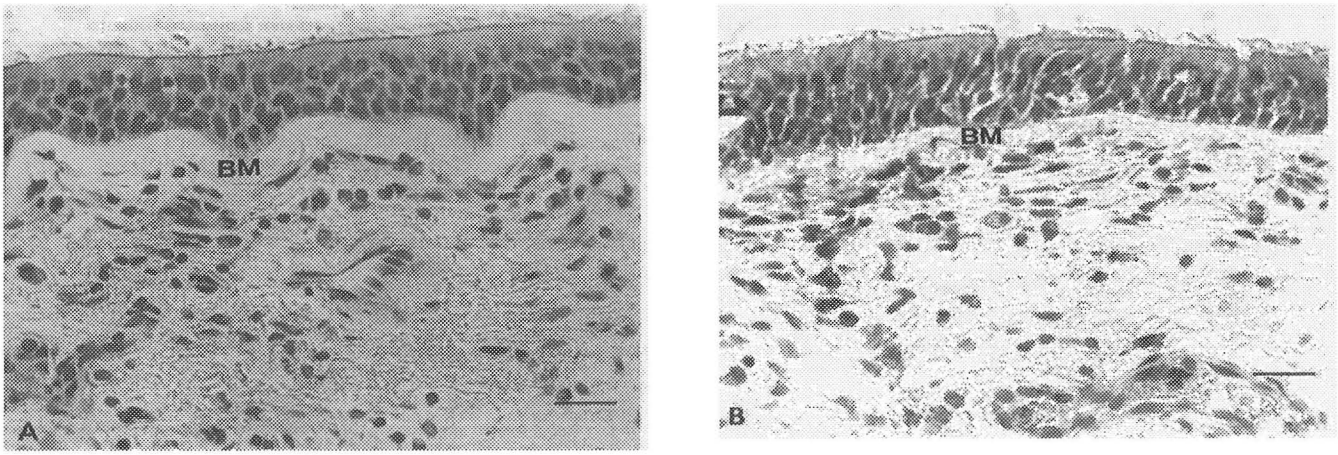

Figure 13: Endobronchial biopsies from a patient with isocyanate asthma. "A" was performed at diagnosis and "B" 6 months post-removal from exposure. The increased thickness of the basement membrane (BM) region has resolved. From Saetta, et al.(10)

above by Saetta et al, using endobronchial biopsies show a reduction in the fibrotic component of airway wall remodeling but no change in the intensity of the inflammatory infiltrate or the percentage of degranulated (active) eosinophils up to 18 months after removal.(10, 115) Persistent inflammation is seen in sputum even decades after removal from exposure and is correlated with persistent bronchial hyperreactivity.(222) The mechanism of persistent bronchial wall inflammation even after removal from exposure is still unknown but is an extremely important research question.

Conclusions:

Occupational asthma is a common disease. It is the most commonly reported occupational lung disease in industrialized nations and it accounts for a significant portion of all adult asthma. Clinically, occupational asthma is a challenging disease both to diagnose and to treat. Diagnosis typically requires multiple steps including demonstration of reversible airflow obstruction or bronchial hyperreactivity and demonstration that one or both are worse at work.

The cornerstone of treatment remains removal from exposure. Despite this every effort should be made to confirm the diagnosis prior to removal. This is important as it is often difficult to establish the diagnosis after one is removed, and the treatment (i.e. removal from exposure) oftentimes has significant implications for the patient's livelihood. Unfortunately, the majority of patients have persistent disease even after removal and pharmacologic treatment is also required.

From a research perspective occupational asthma has much to teach us regarding asthma in general. It offers several advantages for the study of the genes involved in asthma pathogenesis and of the genes important for the prognosis of asthma. Genetic studies in occupational asthma have helped confirm the functional importance of HLA polymorphisms to disease development. In addition, studies in occupational asthma unequivocally demonstrate the importance of exposure dose in the development of both sensitization and disease and the importance of exposure avoidance in the treatment of asthma. Occupational asthma also provided some of the first insights into the potential importance of exposure routes other than the respiratory tract. More importantly, occupational asthma shows us that asthma may be a preventable illness. Exposure reduction has reduced the burden of disease in several industries and it may even be possible to define a threshold exposure dose below which sensitization does not occur. However, occupational asthma also provided some of the first evidence that once developed, asthma is not a completely reversible disease. We still don't know why the disease persists but occupational asthma also shows us that irreversible scarring in the airway wall is probably not the most important factor determining disease persistence. Thus, many unanswered questions remain regarding the pathogenesis of asthma. Hopefully, with continued research occupational asthma can continue to help us find the answers to these questions.

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