Epidemiological Aspects of Asthma

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Although genes play a role in the pathophysiology of asthma, the genotypic variants that permit the development of asthma are common and lifestyle and environment are the limiting factors determining the prevalence of asthma. There is now strong evidence for a widespread increase in the prevalence of asthma over the last 30 years at least, and evidence is emerging that the prevalence of asthma varies widely between different populations, even in countries that have adopted a “Western lifestyle”. Much of this variation is due to variation in the prevalence of sensitization to common allergens, but the causes of this variation are also unclear. There is an excess mortality in those with asthma, predominantly in the older age group. Attempts to improve the management of the disease through better delivery of services are still largely unevaulated.

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The epidemiology of asthma is relatively poorly understood and much of it is controversial. This review can do no more than sketch in a few of the areas of current interest.

The genetics of asthma is currently the focus of a great deal of attention encouraged by the new genetic technology and the hope that understanding the genes associated with asthma might help to unravel the mechanisms of the disease and hence to provide new treatments. Recent interest has focused on linkage of both a high total IgE phenotype and bronchial reactivity to a marker on Chromosome 5 close to the genes for both IL-4 and IL-5 as well as other possibly relevant gene products (Marsh et al, 1994; Postma et al, 1995). Linkage to Chromosome 11q has also been reported by several groups (Cookson, 1989; van Herderen et al, 1995), though the nature of this linkage is disputed. Sensitization to specific allergens is restricted by the HLA haplotypes of the individuals as shown for several ragweed and rye grass allergens (Marsh et al, 1982), though the relevance of this to the pathogenesis of disease is questioned by the highly polyclonal response to most allergens and the large number of epitopes on any allergen that may lead to sensitization. Other genes of importance may include the beta-receptor gene, variants of which have been associated with night time symptoms, and various T-cell receptor proteins. The importance of genes to the epidemiology of the disease is, however, relatively small. The prevalence of the disease has increased greatly over the years and the variation in prevalence from place to place is considerable. It appears that a large proportion of any population are likely to be susceptible, but that the prevalence of disease is likely to be determined by environmental factors rather than by genetic variation.

Evidence for an increase in asthma prevalence comes from studies which have examined the same populations using the same methods at different times. There is now a large number of such studies worldwide and almost all of them report an increase. Some of these studies can be criticised for not using precisely the same methods, or for studying populations that may have been affected by migration, or studying the prevalence of diagnosed asthma which may have been unduly affected by changes in diagnostic fashion. However, taken together, these studies strongly suggest that the increase is real and can be estimated as about a 5% increase per annum on average. Wide variations in the prevalence of asthma and asthma like symptoms are now also being documented (ECRHS, 1996) and lend support to the view that the prevalence of disease is strongly influenced by the environment.

The increase in asthma has been documented in some stud-
ies alongside an equivalent increase in the prevalence of other atopic diseases such as eczema and hay fever (for instance, Burr et al., 1989) and it is likely that part of the increase at least is due to an increase in the underlying atopic condition. This has been documented more precisely in two studies that have taken serial blood samples from schoolchildren over a number of years and shown that there has been an increase in the prevalence of children in these populations who have IgE against specific common airborne allergens (Gassner, 1992; Nakagomi et al., 1994). It is important to note that in both of these studies the increase in atopy was not due to a particular allergen, but that sensitization had increased to a wide range of allergens.

Although trends in asthma may provide important clues to the nature and causes of the condition, they are difficult to research because of our inability to collect data that are now lost. It is therefore more profitable to consider contemporary variations in the disease between different geographical areas. The most striking of these have, until recently, been seen in the developing countries where very large variations between urban and rural settings have been reported (Anderson, 1978; van Niekerk et al., 1979; Waite et al., 1980; Keeley et al., 1991). Once again these suggest a strong environmental influence on the disease and it is interesting to note that in Keeley’s study of children in the affluent northern suburbs of Harare the black and white children had the same prevalence of exercise induced bronchospasm.

Unfortunately the information from these areas on other risk factors is relatively sparse, particularly with regard to information on atopy, and it is unclear how these populations differ. About twenty years ago a study in Southern Rhodesia showed that total IgE levels in a rural area with no recorded cases of asthma were higher than in an urban population of asthmatics (Merrett et al., 1976). Moreover, though the urban patients with asthma had the highest prevalence of IgE antibodies against dust mites, the rural population had a higher prevalence of these antibodies than the urban population without asthma and they had the highest prevalence of antibodies against meadow grass. This suggests that the main difference is not in the production of IgE antibodies to Aeroallergens, but could be related to the presence of blocking antibodies, from parasites that were endemic in the rural area and which could have prevented the onset of asthma (Godfrey and Graddidge, 1976). This hypothesis is also supported by some studies from South America (Lynch et al., 1987). These show that in low income families there is a low response to skin testing with local house dust but a high sensitivity to ascars. There was also a poor response to a Prausnitz-Küstner test in which donor IgE was injected under the skin and then challenged with allergen. On the other hand the poorer subjects had an equal prevalence of detectable IgE against house dust and did respond to skin challenge with anti-IgE. All of this supports the hypothesis of ‘blocking antibody’ against parasites preventing degranulation of the mast cells by aero-allergens. However, the poorer subjects also had lower levels (though not a lower prevalence) of anti-house dust IgE than the richer sample and this may also have had some relevance.

Differences in the prevalence of disease are also now documented in the western world including marked differences in Germany where the former Eastern Germany has had much lower levels of asthma and bronchial responsiveness. Eastern Germany has also high total IgE levels and a lower prevalence of skin sensitivity. Whether this can also be explained in terms of differences in parasitization is not established, but it is now clearly established that there are large variations in the prevalence of subjects who raise specific IgE to common allergens (ECRHS, in press) and it is also important to understand why this large variation takes place.

There are several reasons for believing that, although contact with allergen is necessary for sensitization to take place, it is not sufficient and is probably not the factor that influences the local prevalence of atopy. First, in both the Swiss and the Japanese studies of schoolchildren, the children were becoming increasingly sensitized to different allergens, not just to a single allergen, but to a wide range of both indoor and outdoor allergens, suggesting that the change was more likely to be due to an underlying increase in susceptibility to sensitization than to an increasing exposure to particular allergens. Secondly, in the European Community Respiratory Health Survey (in press) the prevalence of atopy, defined as the percentage of the population that had IgE to at least one of the allergens tested, was barely affected by the addition of an important local allergen (birch in northern Europe and Parietaria in southern Europe). In Australia where house dust mite sensitivity is of great importance in the humid coastal area of New South Wales it was hypothesised that atopy and asthma would be lower in prevalence in the dry inland areas. However, although the mite levels were comparatively low here, as expected, the prevalence of asthma was higher than in the mite infested areas due to an increased sensitization to pollens and moulds (Britton et al., 1986). Again the prevalence of individual allergens did not seem to greatly alter the overall prevalence of atopy or, in this case, atopic disease.

In a short review it is not possible to enter in detail into the possible reasons why some populations are more likely to become sensitized than others, though some hypotheses that have had popularity in the past are looking like unlikely explanations now. There is little evidence that air pollution induces atopy or asthma (Committee on the Medical Effects of Air Pollution, 1996) and it has seemed a paradox to some that air quality has improved, so the prevalence of asthma has increased (Hsieh and Shen, 1988). Some early evidence suggested that maternal smoking might lead to atopy in children (Magnussen, 1986) but subsequent evidence has been inconsi-
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tent (Sølyseth et al, 1995) suggesting more asthma among the children of mothers who smoke postnatally but, if anything a reduction in atopy in the children of mothers who smoke during pregnancy. Infections in early life were believed to increase the likelihood of sensitization (Frick, 1986) but this view has to be at least modified. Consistent evidence suggests that atopic disease (hayfever and eczema, though not notably asthma) is more common in children who do not have older siblings. It has been suggested that this might be due to an increased infection rate in younger siblings protecting them against atopic disease (Strachan, 1989). Until recently there has been very little evidence to support this hypothesis. Recently, however, a study from Guinea-Bissau has shown that young adults with a well documented history of severe measles were less likely to be sensitized to dust mites (Shaheen et al, 1996).

Turning from the underlying causes to the provoking causes of the disease, the issues are rather simpler. Here undoubtedly exposure to allergen is extremely important. There is abundant experimental and clinical evidence to suggest that challenge with allergen will provoke disease and there is epidemiological evidence to show that those who are sensitized to an allergen have a greatly increased risk of disease if they are exposed to the allergen (Peat, 1994). Another factor that is of very great importance is viral infection, particularly with rhinoviruses and particularly among children. Smoking and air pollution are frequently cited by patients as important provokers of symptoms though the evidence that they have a major effect on clinical disease is relatively poor for patients with asthma.

One aspect of air pollution has probably been underestimat-ed in the past and this is the part played by allergen. The problem lies mainly in the difficulty of assessing allergen exposure from ambient air where the sources and the nature of allergens may be largely unknown. However the powerful effect of allergen has been demonstrated in a number of episodes that have been investigated. These include a number of ‘epidemics’ that have involved local air pollution from plants processing castor bean and the epidemics of asthma caused in Barcelona and elsewhere from pollution by soy bean allergen (Anto et al, 1989). It is informative that the initial report from Barcelona suggested that oxides of nitrogen might be implicated (Ussetti et al, 1983) and it was true that the arrival of asthmatics in casualty departments coincided with an increase in nitrogen oxides in the outside air. However, it was later shown that this was simply a marker of the weather conditions that also allowed the levels of allergen to build up in the air. Other allergens are natural seasonal contaminants and some, such as Alternaria in the northern United States have been implicated in respiratory arrests in young people with asthma in late summer and autumn (O’Holloran et al, 1991).

Death from asthma remains a controversial issue. Population surveys estimating the risk of death among asthmatics are uncommon and come to different conclusions. Studies of 25-64 year olds in the United Kingdom (Markowe et al, 1987) and 25 to 74 year olds in the USA (McWhorter et al, 1989) concluded that the excess mortality was 60% and 20% respectively, with the excess risk of death increasing with age. However, in a complete population cohort of asthmatic patients in Olmsted County there was no excess of deaths except in those who had another lung disease in addition to asthma (Silverstein et al 1994). By contrast studies from life assurance companies suggest that those said to have asthma do indeed have an excess risk, in contrast to those who report allergies but no asthma, who have a reduced risk of death (Brackenridge, 1990). The nature of the excess risk is poorly understood as is the relation of ‘asthma’ to decline in lung function with age.

The relation between asthma mortality and treatment is a perennial source of controversy. In 1948 Benson and Perlman reported that asthmatic patients using adrenaline sprays which they obtained from travelling salesmen against the advice of their doctors had a 70% excess risk of death (Benson and Perlman, 1948). In the 1960s there was a marked increase in asthma deaths in some countries which was attributed to the sales of high dose isoproterenol inhalers (Stolley and Schinnar, 1978). Nevertheless the sales of other more specific beta-2 agonists increased in the years following. In the mid to late 1970s there was another very marked rise in deaths in New Zealand. This increase was attributed to the increased use of another high dose inhaler, fenoterol, and withdrawal of the drug in New Zealand coincided with the end of the epidemic (Pearce et al, 1995). Other researchers, while agreeing that sales of high dose beta-agonists in large quantities was associated with deaths from the asthma argued that the association could be due to more severe asthmatics using more, and more potent, beta agonists. The role of beta agonists in precipitating asthma deaths is still unclear though it is generally agreed on the one hand that high doses are at least a marker of risk, and on the other hand that places which never licensed fenoterol also saw an increase in deaths from asthma starting in the mid 1970s. In Great Britain, for instance, which had relatively little penetration by this specific drug the mortality rate from asthma doubled between the mid-1970s and the mid-1980s before halving again in the subsequent decade. A further aspect of treatment that has almost certainly been important is the increasing use of inhaled steroids in many countries and these have been associated with reduced fatality rates (Ernst et al, 1992).

Recommendations that physicians should be careful about prescribing large amounts of beta-agonists without steroids are now being incorporated into guidelines for the management of asthma. These guidelines are being widely disseminated though their evaluation is still incomplete.
REFERENCES


