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Editorial

Asthma: epidemics and epidemiology

A recent editorial in *Thorax* challenged its readers with an interest in the aetiology of asthma to investigate potential causative agents in the environment using epidemiological methods.[1] The aetiology of scurvy, it was argued, was established readily enough from a recognition in population studies that the disease was associated with a lack of fresh fruit and vegetables. Epidemiological tools for investigating asthma have, however, been available for some time, and yet its aetiology remains a major puzzle. Furthermore, its incidence and mortality appear to be rising despite considerable advances in the development of efficacious medication.[2–5]

The explanation for this paradox must lie with environmental rather than genetic factors, as was argued in the editorial. When asthma occurs in an identical twin the concordance rate is, after all, only 19%[6]; and when immigrants from underdeveloped countries adopt a Western lifestyle their formerly low risk of developing asthma is exchanged for the high risk of their new communities. Changing concepts in definition may have exaggerated the true degree of the increase in asthma prevalences in Western countries, but a greater readiness to diagnose asthma in those with unduly irritable airways (or to give asthma as the cause of death in asthmatic individuals who die suddenly and are not subjected to necropsy) seems not to be the whole answer. What then is afoot in the environment and why have epidemiologists experienced great difficulty over its identification?

A tool of particular value to the epidemiologist is an epidemic, as it provides an opportunity of identifying a specific environmental agent of aetiological importance. This in turn may lead to clarification of relevant mechanisms. Many epidemics of asthma have, however, been recorded without identification of such an agent. Recent reports from Barcelona linking epidemics of asthma with the release of airborne dust from ships unloading soybean are consequently of considerable interest.[7–11]

Epidemics of asthma in Barcelona

During the years 1981–4 there were eight separate days on which the numbers of referrals for emergency treatment of asthma to urban hospitals in Barcelona were so far above average that the services were overwhelmed. As a result a collaborative research group of epidemiologists, physicians, botanists and meteorologists was established, and its members embarked on a classic series of epidemiological investigations. Records revealed no convincing relation to conventional measures of urban air pollution or viral epidemics, but these earlier outbreaks showed close clustering in both time and space, suggesting a point source in the harbour district of the city.

Prospective monitoring of emergency admissions of adults (more than 14 years of age) for asthma to four city hospitals was arranged for 1985 and 1986, and the investigators defined admission days of particular interest, following guidelines proposed in earlier investigations of epidemic asthma in the cities of New York and New Orleans.[12] On an "unusual asthma day" the number of admissions would exceed the average over a contemporary period of 15 days by such a degree that the probability of chance was less than 2·5%. When in addition there was clustering within a four hour period within the unusual asthma day by such a degree that the probability of chance was less than 5%, an "asthma epidemic day" would be defined. Suspecting the possible relevance of atmospheric emissions associated with loading or unloading ships in the harbour, the investigators also recorded the types of cargo moved on any given day and sampled airborne particulate contaminants within the suburbs served by the participating hospitals.

In the event, 1985–6 produced 23 unusual asthma days, of which 13 were asthma epidemic days. All 13 coincided with the unloading of soybean and the risk ratio—that is, number of asthma epidemics on soybean movement days (13/262): number of asthma epidemics on days without soybean movement (0/468)—was too great to quantify (lower limit of 95% confidence interval 7·2). Furthermore, retrospective review of harbour records showed that all the previous outbreaks noted from 1981 had also occurred on soybean movement days. Of 25 other cargoes moved on at least one asthma epidemic day during 1985–6, only wheat gave a risk ratio significantly greater than 1. Wheat, however, was moved on only three of the 13 asthma epidemic days, and when the confounding effect of handling soybean was taken into account the

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association with wheat was no longer statistically significant.

The epidemiological data thus suggested that airborne dust was being released into the city environment in association with the unloading of soybean and that this was causing the outbreaks of asthma. That this was plausible was confirmed by the meteorologists and botanists of the research team. All epidemics occurred on days of high barometric pressure and little wind, the city lying downwind on every occasion on which air movement occurred. Ambient temperature and humidity were not found to exert any effect. The samplers showed many cellular particles characteristic of soybean wall cells, and starch was identified chemically. Similar particles were noted in dust samples taken from the holds of ships carrying soybean.

Of considerable importance was the observation that all soybean was unloaed into one of two silos, A or B. A suction process delivered material to the top of each silo, which was then filled by gravity alone. Silo A was closer to the city than silo B and much taller (70 compared with 20 metres). It also had an open top through which dust could readily escape. Silo B, on the other hand, was fitted with bag filters which inhibited escape of dust. Only silo A proved to be significantly associated with the epidemics of asthma. Filters were consequently fitted to silo A and with this simple manoeuvre epidemic asthma in Barcelona appears to be at an end.

During 1981–6 there was a total of 26 outbreaks affecting 687 people and 1155 emergency admissions to the collaborating hospitals—a not inconsequential burden on the facilities available. It is not clear whether those affected already had asthma, which was merely triggered by intermittent exposures to soybean dust, or whether these exposures were primarily responsible for inducing the asthmatic state. The latter would of course contribute to a rising incidence of the disease.

Soybean is a known but not common cause of occupational asthma, which prompts the question of whether it is a more potent asthma inducer than was previously recognised or whether the exposure doses were inordinately high in the Barcelona epidemics. Alternatively, the responsible agent may have been a contaminant rather than the soybean itself. The Barcelona investigators believe that soybean alone was responsible and there are good arguments to support this. Contaminating microbes, fungicides and pesticides are not likely to appear exclusively in dust from soybean cargoes, though conceivably there could be an arthropod parasite specific to soybean—as occurs with certain types of grain.

In favour of specific immunological hypersensitivity to soybean itself was the striking difference in prevalence, in a case-control study of positive responses to radioallergosorbent tests (RASTs) with commercial soybean antigen extracts, between asthmatic subjects admitted during the epidemics (74% positive) and those admitted at other times (4·6%).[10] This is consistent with the observation that the country of origin of the soybean, which could well affect the nature and level of contamination, had no effect epidemiologically on the pattern of response. On the other hand, the investigators found the relation between epidemic cases and positive RAST responses was stronger with extracts of soybean dusts taken from Barcelona harbour (which are more likely to contain contaminants) than with the commercial extracts. The observation that epidemics were related to soybean in bulk form but not in meal or pellet form could be explained either by a lesser likelihood of contamination of the meal and pellets or by these forms having a lesser propensity to produce airborne dust.

Other epidemics of asthma

The investigations in Barcelona provide convincing evidence of a causal relationship between a specific airborne environmental pollutant, soybean dust, and epidemics of asthma. Such evidence has been surprisingly rare since Charles Blackley first showed that seasonal exacerbations of asthma could be related to the seasonal release of airborne pollens, though epidemics attributable to air pollution with castor bean dust have been described.[13,14] In the city of New Orleans epidemics of asthma remarkably similar in pattern to those in Barcelona were encountered during the 1950s and 1960s, but their precise cause was never fully explained. Suspicion fell chiefly on grain dust released from its own port (thereby closely simulating the circumstances in Barcelona), neighbouring fire smoke emissions, and "natural inhalant allergens acting in seasonal patterns."[15] The epidemics were reported only from the Charity Hospital, the single major source of free emergency care, and were observed on unusually cold days when there was atmospheric stagnation. Their apparent disappearance in the 1970s probably owed as much to the increasingly widespread use of effective medications, which previously were not readily available to the indigent sections of the population, as it did to any change in the environment.

More recently, in Birmingham there was a two day outbreak of asthma that was tentatively attributed to hypersensitivity to airborne fungal spores.[16] This was largely because high concentrations of *Didymella exitialis* and *Sporobolomyces* spp were observed at the time, but subsequent immunological studies provided no supporting evidence of hypersensitivity. The outbreak did, however, occur at the time of a thunder-

storm—an association that has been reported anecdotally from Africa. The explanation is far from clear, though a lack of regular prophylactic medication may be an important factor behind the apparently greater impact in underdeveloped countries.

More dramatic epidemics of respiratory illness, associated with high mortality, occurred when urban atmospheric pollution from burning fossil fuel was at its worst (that is, at times of prolonged temperature inversion and trapped, stationary air over major industrial areas) and when this coincided with unusually low temperatures or viral infections, or both. It is not always possible to identify deaths specifically attributable to asthma in such epidemics, though some are likely to have occurred. It is clear, however, that in the notorious London fog of 5–9 December 1952 the major burden fell on the elderly with smoking induced chronic airflow obstruction or cardiac disease.[17]

Asthma may, of course, occur in epidemic proportions in occupational settings, where specific asthma inducers of both organic and chemical origin are known to be responsible. Most commonly only the occasional worker is affected, but with unduly high levels of exposure (especially accidents) and with agents of particular potency (for example, platinum salts, detergent enzymes, microbially contaminated humidifiers) prevalences of the order of 20–50% have been observed in some workforces.[18–20]

Asthma in the population at large

If asthma associated with epidemics is to provide useful clues to the aetiology of asthma in the population at large, identical or similar causative agents must be exerting substantial effects, or the mechanisms that operate in epidemics must be of general relevance (or both). The Barcelona studies suggest that a single newly introduced organic allergen dispersed in the air caused widespread sensitisation in the local population and recurring attacks of asthma whenever exposure levels reached a sufficient level. It may conceivably have induced asthma in subjects who were previously unaffected, and there may be a close parallel with allergenic pollens and mould spores currently distributed in the environment.

An increasing incidence of asthma in the population at large could thus be a consequence of increasing concentrations of aeroallergens or, more likely, of the introduction of different or more potent airborne allergens as agricultural methods evolve and new crops such as rape and soybean are cultivated or imported. Maybe a changing composition of aeroallergens poses the greatest threat, children having an innate ability to develop tolerance that adults do not retain. Thus children, but not adults, tend to "grow out of asthma" and children were not obviously affected by the Barcelona epidemics. If adults, by contrast, are less able to develop this tolerance, they would become more vulnerable to asthma in developed than in underdeveloped countries—either from changes within the local environment or from domestic moves from one environment to another.

The evidence from the disasters associated with fossil fuel air pollution suggests that the influence of the environment is multifactorial and that important interactions operate. Whereas the risk from low ambient temperatures, viral infections, aeroallergens, smoke particulates, sulphur dioxide, and other industrial emissions may be relatively trivial individually, their combined effects may be formidable. Several mechanisms could be important. Viral infections and oxidant air pollutants (ozone and oxides of nitrogen) may increase baseline levels of non-specific bronchial responsiveness, as may seasonal exposure to pollens and mould spores in sensitised individuals.[21–23] Once non-specific bronchial responsiveness is increased sufficiently any bronchial irritant could provoke asthmatic reactions, and the threshold for specific hypersensitivity responses to environmental allergens or occupational agents will be diminished. Furthermore, late reactions to environmental allergens or occupational agents may be expected to produce additional increases in the levels of non-specific bronchial responsiveness, thereby creating a cycle of escalating vulnerability.

Such environmental challenges need not be exclusively airborne. Ingested soybean, for example, will provoke asthmatic reactions in some (though not many) individuals, as may many other foodstuffs. Most food allergens are encountered solely via the gastrointestinal tract, implying that a proportion of molecules survive the denaturing processes of cooking and digestion without loss of antigenic potential. The finding of positive RAST and skinprick test responses to such foodstuffs confirms that this is so, and many macromolecules are now known to cross the intestinal tract antigenically intact. Some may then be identified in the milk of nursing mothers, whose infants may suffer allergic symptoms as a consequence. Food allergens such as soybean, wheat and other cereals, avian proteins, and yeast may thus challenge the human body through both the gut and the lungs. Either route may lead to sensitisation, though once immunologically mature the gut is less vulnerable to this development. There is the possibility therefore that, once an individual is sensitised via the lung, asthmatic reactions could be provoked by an unsuspected gastrointestinal challenge—and vice versa. There is also the possibility that challenges occurring simultaneously or in quick succession from the two separate routes could produce an unusually strong

response. This was observed when an antibiotic worker with occupational asthma attributable to airborne penicillin dusts was investigated in sequence first by oral and then by inhalation challenge.[24]

Milk, egg, and wheat, along with food additives such as preservatives or colouring and flavouring materials, are said to provide the greatest food threat to those with asthma.[25] They are widely used in "fast food" and could be relevant to current trends in the epidemiology of asthma. So too could the increasing use of aspirin and other non-steroidal anti-inflammatory agents. More intriguing is the possible relevance of dietary salt. It has recently been suggested that differences in the prevalence of asthma in geographically distinct populations of Britain could be attributed to differences in individual salt intake, higher turnover rates of dietary sodium somehow being associated with higher levels of non-specific bronchial responsiveness.[26,27]

A further individual trait undergoing change at present is cigarette smoking. This too could prove to be relevant to asthma, though the nature of the relation is far from clear. On the one hand, smoking stimulates IgE production, is correlated with the degree of non-specific bronchial responsiveness, and appears to be a risk factor for some types of occupational asthma—perhaps those associated with IgE responses.[28] On the other hand, it is a common experience to hear of asthma that develops or worsens after cessation of smoking, and in other populations experiencing occupational asthma the non-smokers have been disproportionately affected.[29] Extrinsic allergic alveolitis and sarcoidosis appear to be similarly more troublesome in non-smokers than smokers, suggesting that tobacco smoke exerts a suppressive effect on the immunological processes (other than IgE production) that have a role in these disorders.[30,31]

Asthma, like coronary artery disease, is largely a consequence of Western civilisation, and like coronary artery disease is related to many environmental factors of aetiological importance. Air pollution resulting from the widespread domestic and industrial combustion of fossil fuels containing sulphur has been greatly reduced during recent decades and cannot be an important factor in the currently observed trends towards an increasing incidence and severity of asthma. Newer, or changing, airborne pollutants, whether of organic or of chemical origin, may be less innocent (especially those in the workplace), and there may be crucial interactions with changing dietary and smoking customs that are catalysed by low ambient temperatures. Definitions and clinical awareness change too, however, and study methods have been far from uniform across different groups of investigators. These problems are likely to have exerted their own influences on apparent secular trends and conceivably the perceived rise in the incidence of asthma is purely artefactual. It is interesting therefore that the latest British statistics for annual deaths from asthma show a small decline—the first for a decade.

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