Asthma outbreaks: an opportunity for research?

Outbreaks of asthma typically consisting of up to hundreds of attendances at emergency departments by patients with unstable asthma, including one or two deaths within a few hours, in specific locations, have been repeatedly reported in the literature. Although respiratory physicians would readily accept the importance of studying both the occurrence and the aetiology of such outbreaks, other professionals and health authorities might not, especially in a context of limited resources.

Asthma is a common condition responsible for a high rate of morbidity and restricted activity. Its prevalence has increased in recent decades and both its causes and the reasons for its increasing prevalence are not well established. Outbreaks of asthma may provide an opportunity for identification of risk factors which are potentially preventable. From a public health point of view, outbreaks of asthma are seen within the context of avoidable morbidity and mortality. A particular outbreak of asthma, or even a series of outbreaks such as occurred in Barcelona with more than 1000 attendances at emergency departments and about 20 deaths, may appear unimpressive in comparison with the larger health burden imposed by many other diseases. In addition, the investigation of asthma outbreaks is difficult and usually requires a retrospective approach. Thus, it is relevant to question to what extent outbreaks of asthma should be investigated.

Review of asthma outbreaks

In 1928 Figley described a time and space cluster of asthma affecting about 200 patients living within a one mile radius of a castor bean mill in Toledo, Ohio, USA. The outbreak was caused by the inhalation of castor bean grinding dust and disappeared after the factory stopped processing castor beans.1 In the 1950s outbreaks of asthma caused by exposure to castor beans were also reported in South Africa2 and Brazil.3

Series of asthma outbreaks have been reported both in New Orleans and in New York.4 The city of New Orleans experienced repeated outbreaks for nearly two decades, most of them involving about 100 attendances at the Charity Hospital emergency department.4 After considering several point source hypotheses it was postulated that the outbreaks resulted from sensitisation of the local atopic population to different seasonal aeroallergens.5 A subsequent decline in the occurrence of asthma epidemics was attributed both to better socioeconomic conditions and the availability of improved medical care for indigent patients.7 By contrast, outbreaks of asthma in New York were not spontaneously identified but were observed during an analysis to identify health indicators for air pollution studies. Although the epidemic days in New York fulfilled a well established statistical definition, they were smaller than the outbreaks mentioned above. No relation was found with air pollution and the days of high asthma incidence were more likely to coincide with Sundays, Mondays, Thanksgiving days, and the subsequent days, leading the authors to propose that exposure to indoor environmental agents might have been important.8 The days of high asthma incidence identified in New York probably reflect a tendency for time clustering of asthma, rather than individual clusters.

In 1985 Packe and Ayres reported an asthma outbreak involving about 80 patients treated in eight acute hospitals in Birmingham.9 This cluster coincided with a thunderstorm. The levels of chemical air pollution were low but there was a large increase in the levels of airborne fungal spores, especially Didymella exitialis and Sponabolomyces, around the time of the outbreak.9 A firm aetiological conclusion was not reached, and the association with the thunderstorm was not tested in a time series design. However, substantial information linking asthma with thunderstorms has been reported from Melbourne, Australia. Outbreaks of asthma coinciding with thunderstorms were first reported there by Morrison in 196010 and by Egan in 1985.11 More recently two further similar outbreaks were reported in Melbourne after thunderstorms, leading to the hypothesis that pollen grains are ruptured in rainwater by osmotic shock, each grain releasing about 700 starch granules small enough to enter the airways.12 The Melbourne researchers have shown that rye grass pollen grains contain a large quantity of starch granules which contain Lol p IX and are coated with Lol p 1.12 Twelve patients involved in the epidemic all had positive skin reactions to both standard rye grass pollen and isolated starch granules compared with seven of 13 outpatient controls with asthma (p<0.05); four of the epidemic cases showed early bronchial constriction after voluntary re-exposure to starch granules.12 The levels of chemical air pollution on epidemic days were below or similar to the levels in a control period.12 While this is a relevant and well established hypothesis, sufficient aetiological evidence has not yet been provided. The association between thunderstorms and asthma in Melbourne, although likely to be real, is still anecdotal as it has also not been studied in a formal time series analysis with complete ascertainment of epidemic days. The case control study was intended only to test the epidemic asthma cases from one single hospital out of the 300 or so patients affected, and the controls were selected from an outpatient department where the association between epidemic asthma and starch allergy was not adjusted for potential confounders such as atopy.

Another outbreak of asthma following a thunderstorm has recently been reported in London.13 The preliminary data suggest that the increased admissions to emergency departments for asthma totalled about 1000 in a period of two days, possibly the largest outbreak ever recorded13 (K Venables, personal communication). The coincidence of outbreaks of asthma with thunderstorms allows the Birmingham and Melbourne hypotheses to be examined again, and a large multidisciplinary study group has been established.

In Barcelona five outbreaks of asthma were reported from a single hospital (Hospital Clinic) between 1981 and 1983. The potential link with air pollution and local public health interest allowed a collaborative group to be established with the aims of long term research and follow up.14 The asthma outbreaks typically showed a point source distribution and, after rejecting several hypotheses, a possible link with unloading of soybean at the city harbour was established. A causal relation between the unloading of soybean and asthma outbreaks was subsequently established through a time series study of harbour activities, a serum case control study, and an intervention study.15,16 The results of these studies led to the identification of similar outbreaks caused by unloading of soybean in Car-
Asthma outbreaks: an opportunity for research?

The most important reason for investigating outbreaks of asthma is the substantial public health burden which they can impose on a community. The aim of research is the identification of a cause and its potential prevention. Repeated outbreaks are more likely to promote a local research effort which may involve evaluation by the local health authorities and an appreciation of the potential cost may be advisable. In the case of the research into the asthma outbreaks in Barcelona an economical study showed that the benefits of the investigation exceeded their cost (Muirillo C, personal communication).

It may happen that local outbreaks are an index of other previously unrecognised outbreaks. In occupational asthma the identification of outbreaks has frequently been followed by reports of similar previously unidentified cases. This has also been the case in Barcelona where the soybean hypothesis was further corroborated in Cartagena, Spain and probably in New Orleans and Naples. The same could occur if the Melbourne hypothesis is corroborated in London. In such cases the benefits of investigating local outbreaks are likely to go beyond just the local community.

There are other valid reasons for investigating asthma outbreaks, since they are natural experiments in which the epidemiological approach can establish a strong time order sequence between an exposure and its outcome. Time order is a relevant criterion of causality. Most diseases result from constellations of component causes, each one in itself being insufficient to produce the disease. However, as Knox has pointed out, when an outbreak occurs the cases are related to each other through some social or biological mechanism or have a common relation to some other event or circumstance. In the Barcelona outbreaks this common event was the inhalation of soybean dust which constitutes a necessary, although insufficient, cause. The assessment of a common factor used to show a strong association with an epidemic which is stronger as the prevalence of an individual factor is lower in the reference group. The strength of an association is considered another important criterion of causality. In addition, if an aetiological cause is found then other relevant risk factors may be properly assessed. With this approach we have reported an interaction between atopy and smoking in soybean epidemic asthma, reinforcing the evidence of a relation between smoking, occupation, and allergic asthma from occupational studies. Another example of a risk factor that could be assessed in a natural model of epidemic asthma is air pollution. An experimental study suggesting that ozone may potentiate allergic bronchial responsiveness led us to test whether this was the case in the Barcelona outbreaks. Although preliminary analysis suggested that the probability of an asthma outbreak was higher on days with higher levels of air pollution, further analysis has been inconclusive (unpublished data) and the hypothesis is still being tested. Other asthma outbreaks may provide a good opportunity to assess possible synergism between air pollution and allergens within the general level in a population.

Some negative considerations should also be stated. The investigation of clusters of cancer has shown that it may be very difficult to define statistically a cluster and that rare diseases tend to cluster. Some authors have stressed the risk of spending resources on investigating apparent clusters which ultimately are due to chance or to the uneven distribution of risk factors both in time and space (responsible for clustering). Rothman has argued that the study of individual clusters of disease do not offer hopeful prospects for scientific advance.

An opportunity for research

The most important reason for investigating outbreaks of asthma is the substantial public health burden which they can impose on a community. The aim of research is the identification of a cause and its potential prevention. Repeated outbreaks are more likely to promote a local research effort which may involve evaluation by the local health authorities and an appreciation of the potential cost may be advisable. In the case of the research into the asthma outbreaks in Barcelona an economical study showed that the benefits of the investigation exceeded their cost (Muirillo C, personal communication).

It may happen that local outbreaks are an index of other previously unrecognised outbreaks. In occupational asthma the identification of outbreaks has frequently been followed by reports of similar previously unidentified cases. This has also been the case in Barcelona where the soybean hypothesis was further corroborated in Cartagena, Spain and probably in New Orleans and Naples. The same could occur if the Melbourne hypothesis is corroborated in London. In such cases the benefits of investigating local outbreaks are likely to go beyond just the local community.

There are other valid reasons for investigating asthma outbreaks, since they are natural experiments in which the epidemiological approach can establish a strong time order sequence between an exposure and its outcome. Time order is a relevant criterion of causality. Most diseases result from constellations of component causes, each one in itself being insufficient to produce the disease. However, as Knox has pointed out, when an outbreak occurs the cases are related to each other through some social or biological mechanism or have a common relation to some other event or circumstance. In the Barcelona outbreaks this common event was the inhalation of soybean dust which constitutes a necessary, although insufficient, cause. The assessment of a common factor used to show a strong association with an epidemic which is stronger as the prevalence of an individual factor is lower in the reference group. The strength of an association is considered another important criterion of causality. In addition, if an aetiological cause is found then other relevant risk factors may be properly assessed. With this approach we have reported an interaction between atopy and smoking in soybean epidemic asthma, reinforcing the evidence of a relation between smoking, occupation, and allergic asthma from occupational studies. Another example of a risk factor that could be assessed in a natural model of epidemic asthma is air pollution. An experimental study suggesting that ozone may potentiate allergic bronchial responsiveness led us to test whether this was the case in the Barcelona outbreaks. Though preliminary analysis suggested that the probability of an asthma outbreak was higher on days with higher levels of air pollution, further analysis has been inconclusive (unpublished data) and the hypothesis is still being tested. Other asthma outbreaks may provide a good opportunity to assess possible synergism between air pollution and allergens within the general level in a population.

Some negative considerations should also be stated. The investigation of clusters of cancer has shown that it may be very difficult to define statistically a cluster and that rare diseases tend to cluster. Some authors have stressed the risk of spending resources on investigating apparent clusters which ultimately are due to chance or to the uneven distribution of risk factors both in time and space (responsible for clustering). Rothman has argued that the study of individual clusters of disease do not offer hopeful prospects for scientific advance.
further investigation until firm aetiological evidence is established.

The author wishes to thank Dr Kate Venables for her valuable comments. The author was Visiting Principal Fellow at the National Heart and Lung Institute, Royal Brompton Hospital, London, UK, in receipt of a grant from Fondo de Investigacion Sanitaria (94/5838), Spain.

Department of Epidemiology and Public Health, Institut Municipal d’Investigacio Medica, Universitat Autonoma de Barcelona, Dr Aguiader 80, 08003 Barcelona, Spain.

J OSEP M ANTO

1 Figley KD, Elrod RH. Endemic asthma due to castor bean dust. JAMA 1928;90:79-82.
3 Ordman D. An outbreak of bronchial asthma in South Africa, affecting more than 200 persons, caused by castor bean dust from an oil-processing factory. Int Arch Allergy 1955;7:10-24.