

Editorial

Contaminated humidifiers and the lung

In 1970 Banaszak and colleagues described four office workers from a total of 27 who complained either of intermittent chills, fever, malaise, aches and pains, cough, and breathlessness or of a more persistent cough and breathlessness alone.¹ The more acute symptoms generally began towards the end of each work day and regressed within 12 hours. All the symptoms were less obvious at weekends and all subsided completely during holidays. The presence of auscultatory crackles, diffuse interstitial abnormalities on the chest radiograph, a restrictive ventilatory defect (with increase in residual volume), and impairment of gas transfer in some, but not all, of these subjects provided powerful supporting evidence for a diagnosis of occupational extrinsic allergic alveolitis. Transbronchial biopsy in one subject confirmed the presence of alveolitis, but the working environment contained no obvious organic dust. The answer was found to lie with the office humidifier and air conditioner. Scrapings from the heating coil over which the newly moistened air was passed produced *Micropolyspora faeni* on culture at 56°C, while sera from each of the affected subjects contained precipitins to the same organism. An inhalation provocation test was carried out in one of the affected people with an extract of the cultured organism, and the clinical features of the disorder were reproduced. The air conditioning process was then modified radically and all these symptoms ceased.

These authors had no doubt that they were observing a new cause of extrinsic allergic alveolitis (humidifier lung), but there was a novel feature to which they drew attention—the absence of an aetiological agent in particulate (dust) form. A further point of some interest is that all four affected workers were non-smokers. Subsequent investigations from many different countries have confirmed the validity of these observations, and it is now clear that both occupational and domestic environments are readily vulnerable to contamination with a variety of water borne microorganisms that pose a threat of hypersensitivity (or toxic) responses in substantial proportions of exposed populations without any risk of infection.

The greatest threat is from humidifiers which draw contaminated water from large and relatively stagnant sources and dispense it in nebulised form in forced air ventilation systems. The microorganisms probably originate from the ambient air itself, but proliferate on the nutrients of the water reservoirs. Their eradication is not always an easy matter. The use of fresh water rather than recirculated water may offer an effective but expensive remedy, while the use of sterilising agents has proved to be disappointing. In many instances a heavily contaminated slime or sludge accumulates within humidifiers or water dependent cooling systems, and this can be removed or reduced by thorough cleaning. The benefit gained is usually temporary, however, and the initial microbial load reaccumulates within a few months.

Appreciable exposure may also arise by accident in the absence of a purpose built humidifier. The most spectacular example of this comes from a Finnish community which obtained its water supply from a nearby lake heavily contaminated with microorganisms. More than 100 of the 750 adults experienced typical symptoms of malaise, fever, cough, and breathlessness three to six hours after sauna, showering, or even dish washing.² Other accidental or incidental exposures have followed leaks from water pipes, the use of water as a cooling agent in air conditioners of buildings and cars (or its condensation in these conditioners), and the ducting of humidified "exhaust" air from water operated vacuum pumps into the main working environment.³⁻⁶

A paradox arises in many cities in the United States, where air conditioning serves to dry as well as cool ambient air. In many buildings, fibre glass insulation is installed inside rather than outside the major distributing ducts. These are rectangular in cross section and are more conveniently transported with the fragile insulating material protected inside. Water may then condense within these ducts as the air is cooled. It is absorbed by the fibre glass, which seems to produce ideal conditions for luxuriant microbial growth. The dehumidified air forced through these ducts is therefore a further potential cause of "humidifier lung."

Like Banaszak *et al*, subsequent investigators have recognised that clearcut evidence of lung disorder is not always present, and that many affected

individuals have the acute systemic symptoms in isolation. Some consequently prefer the term "humidifier fever," or even "humidifier disease" since fever itself cannot always be documented. It has also become clear that various contaminating microorganisms, not necessarily thermophilic, are likely to be responsible. Characteristically, numerous bacteria, fungi, and even protozoa are found in the contaminated water; and multiple precipitin responses are observed in the sera of exposed subjects whether they appear to be affected or not. Whether responsibility lies with a single microbial species or with many is consequently difficult to determine.

This lack of diagnostic specificity is, of course, a feature of the precipitin response in extrinsic allergic alveolitis, and is a prominent finding in the increasing evidence that type 3 (Arthus) hypersensitivity is not primarily responsible. The granulomatous response which is observed histologically most favours type 4 (cell mediated) hypersensitivity, and this is supported by failures to confirm either immune complex disposition or the presence of vasculitis. The time course of the acute "systemic" response is nevertheless suggestive of type 3 hypersensitivity or toxæmia, and in the context of humidifiers we may reasonably consider whether different processes are in operation and whether humidifier lung and humidifier fever are distinct disorders.

The clinical features of humidifier fever are not readily distinguished from grain fever in grain workers or the Monday fever of cotton workers. Nor are they clearly distinct from metal fume fever, serum sickness, or even influenza. These diverse causes suggest that the end response is non-specific and may be provoked through various mechanisms. One suggestion that has generated a good deal of interest is that endotoxins from Gram negative bacteria cause Monday fever and humidifier fever by activating complement by the alternative pathway.^{7,8} Adequate concentrations of endotoxin appear to be liberated into the appropriate environments, and similar symptoms have been provoked by inhalation provocation tests using purified endotoxin.⁹ They have also been provoked in experimental cotton carding rooms—not only in cotton workers with byssinosis but in a proportion of volunteers without apparent previous exposure.¹⁰ Not all were affected, suggesting that differences in threshold exist in the population at large; and not all with symptoms showed altered lung function. When changes occurred they were indicative of airway obstruction rather than parenchymal dysfunction.

Inhalation provocation tests with endotoxin-free bird serum in subjects with bird fancier's lung pro-

duce an identical systemic febrile response, which may or may not be associated with convincing evidence of a response in the lung itself.¹¹ The higher the dose the more likely a change in lung function. From these observations we could argue that the systemic response is simply a more sensitive indicator of extrinsic allergic alveolitis than the alveolar response but is an integral part of the disease. In that case clearcut pulmonary dysfunction should eventually become manifest in all cases of humidifier fever if exposure is sufficiently strong and prolonged. Alternatively, the absence of systemic symptoms in the chronic form of extrinsic allergic alveolitis and differences in time course between acute systemic and acute pulmonary responses (gas transfer may continue to decline after recovery from the systemic response begins) support the idea that humidifier fever is a separate disorder. Whatever the answer, it is interesting that radiographic abnormalities have been uncommon in subjects with humidifier fever associated with respiratory symptoms, especially in those reported from Britain. Since the acute form of extrinsic allergic alveolitis is also rarely associated with radiographic abnormalities unless exposure is unduly heavy or prolonged, this may reflect a lesser tendency of the "humidifier" antigens to produce the chronic form of extrinsic allergic alveolitis. It has been postulated that this is a consequence of inhaling the causative agent in soluble rather than particulate form. When contamination is by thermophilic actinomycetes, however, radiographic abnormalities are not uncommon. Furthermore, two groups of British investigators have recently reported radiographic abnormalities typical of extrinsic allergic alveolitis in subjects with humidifier lung not related to thermophilic organisms—both in this issue of *Thorax*.^{12,13}

While humidifier fever may or may not be a forme fruste of extrinsic allergic alveolitis, there is no doubt that humidifier asthma, described for the first time on page 248, deserves separate recognition. It is perhaps surprising, that asthma has not been identified before in association with contaminated humidifiers—as the authors point out. Extrinsic allergic alveolitis is associated with bronchial hyper-reactivity and most (if not all) of its aetiological agents are known to cause asthma as well. The prevalence found by Burge *et al* in their survey was similar to that of humidifier fever, which implies that contamination of humidifiers is likely to become an important cause of occupational asthma.

Burge and his colleagues draw attention to two further interesting features of the disorders associated with contaminated humidifiers—the prominence of symptoms in some workers on the first day back at work, and the negative association with

cigarette smoking.¹⁴ The former is a classical characteristic of byssinosis and this gives some support to the suggestion that humidifier fever shares with it an aetiological agent to which the body develops rapid but transitory tolerance—for example, bacterial endotoxins. It is not unknown, however, for more conventional types of occupational asthma, including those induced by microbially uncontaminated low molecular weight chemicals, to be most troublesome on the initial work day after a break from continual exposure, and it is by no means unusual for byssinosis and the humidifier disorders to be active throughout the working week. This characteristic of byssinosis may consequently be much less specific than is generally supposed. This fuels the controversy over whether byssinosis is merely an example of occupational asthma.

The parallel between byssinosis and humidifier fever and asthma is actually quite close, though there is currently no evidence of extrinsic allergic alveolitis in the cotton industry. Dust from unwashed cotton is often heavily contaminated with microbes and some investigators have found symptoms and decrements in ventilatory function to correlate more closely with microbial (or endotoxin) concentrations in the working environment than with the overall concentration of respirable dust. As with humidifier fever, Monday fever in cotton workers is not invariably associated with any appreciable change in lung function. Groups of affected workers do, however, show significant work related decrements in forced expiratory flow by comparison with unaffected colleagues, and there is a widespread assumption that workers with Monday fever will eventually develop airway obstruction. This could be challenged, as could the assumption that reversible airway obstruction on Mondays (byssinosis grade 1) leads to chronic obstruction (byssinosis grade 3) if exposure continues.¹⁵ The implication here is that chronic airway obstruction in cotton workers could be an independent problem, and one which is strongly enhanced by smoking. This suggestion is more compatible with current conclusions in the grain industry, where grain fever has been found to be largely unassociated with acute airway obstruction and where chronic exposure to grain dust and to cigarette smoke probably contribute additively to chronic airway obstruction.^{16,17} It will be interesting to see whether a similar risk will be discovered in workers chronically exposed to contaminated humidifiers.

The possible relevance of smoking to the acute (and probably allergic) disorders associated with occupational exposure to these organic agents is rather different. Cigarette smoking is now known to impair precipitin responses to several organic anti-

gens, and this appears to be associated with a diminished risk of both extrinsic allergic alveolitis and occupational asthma.¹⁸⁻²¹ This is well illustrated by the disorders associated with humidifiers. There is a potential selection bias, however, because smokers and precipitin negative workers are less likely to be subjected to thorough investigation. The strength of this negative association therefore remains to be established.

The range of disorders induced by contaminated humidifiers is certainly a broad and interesting one. It encompasses almost the entire field of respiratory disorders that follow the inhalation of organic agents, and this will surely stimulate valuable continuing research.

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