CORRESPONDENCE

Haemolytic anaemia in a case of occupational asthma due to maleic anhydride

Sir,—The short report by Gannon et al (1992;49:142–3) is misleading in two important respects. In our view the patient did not have occupational asthma and there is insufficient evidence of a relation between his exposure to maleic anhydride and the development of haemolytic anaemia to suggest a hitherto unrecognised toxic effect of maleic anhydride.

The patient is atopic and there is some documentary evidence of childhood asthma although he does not recall this. During the first few days of his work on the maleic anhydride plant in 1961 he had an episode of bronchospasm almost certainly as a reaction to heavy exposure to fume, including maleic anhydride among other irritants. This must be presumed to have been an irritant response as he had not had sufficient exposure to have acquired immunological hypersensitivity. He was removed from heavy exposure on the manufacturing plant but then worked in laboratory environments where he continued to have substantial exposure to maleic anhydride for a further 15 years. There was also some exposure to phthalic anhydride during this period. Nevertheless, at no time did he report to his family doctor or to the works medical department with symptoms of asthma. In fact there is no record of his attendance at the medical department for any reason during this period. IgE concentrations were not measured until after his two haemolytic episodes when they were found to be raised. This probably only reflects exposure; a study now in progress indicates that about 15% of those exposed to maleic anhydride show, by RAST, IgE binding to human serum albumin-maleic anhydride conjugates without any respiratory symptoms.

Clinical asthma first developed in this patient soon after his return to work after his first haemolytic episode. This was before he resumed a work pattern that would have increased his exposure to maleic anhydride (see figure). When, in fact, his exposure did increase his asthmatic symptoms did not get worse. On the other hand they persisted after his second haemolytic episode despite his having ceased work at the factory. He lives about 8 km from the works and significant exposures from gaseous emissions are hardly credible.

Autoimmune haemolytic anaemia is normally cryptogenic. No external causative agent is detectable in most cases although a few medicaments have been associated with it. In this case the first episode had been preceded by an illness presenting with malaise, tiredness, weakness, headache, and shivering. Any presumptions about a cause for his haemolysis, if it existed, must be speculative. Logically, however, a preceding viral illness would seem to be at least as likely a precipitating factor as a chemical substance.

It is, of course, impossible to exclude maleic anhydride as the causative agent. We believe the connection is unlikely because: (1) there were many years of exposure to maleic anhydride before his first episode of anaemia; (2) there were no haemolytic antibodies to red cell-maleic anhydride complexes; (3) there is no similarity whatsoever between the pulmonary haemorrhagic and haemolytic condition associated with trimellitic anhydride and the pathology in this case.

In the unlikely event of his haemolytic anaemia being caused by maleic anhydride in our view there was no demonstrable additional association with occupational asthma. Although his second episode of anaemia occurred after his return to shift work with its attendant increased exposure to maleic anhydride his asthma preceded this by several weeks. The time relations are shown in the figure.

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The Authors’ reply

The one clinical fact about which we agree with Jackson and Jones is that this man is highly sensitised to maleic anhydride with extremely positive IgE antibodies to maleic anhydride: human serum albumin conjugate.

The basis of diagnosis of occupational asthma in this case was from the history of asthmatic symptoms deteriorating at work and improving away from work, which is the usual method of making this diagnosis. It is correct to suggest that in general allergic reactions do not occur with the first exposure and a period of exposure without symptoms would usually be expected; however, sensitisation may be induced by a single large exposure. Once sensitised, very small exposures can elicit symptoms. It is quite likely that exposures could be sufficient to cause asthma in a sensitised subject without haemolysis or that the immunological mechanisms responsible for the haemolysis took longer to develop. A similar situation occurs in patients with asthma and alveolitis, where much larger exposures are required to elicit the alveolitis. The persistence of asthmatic symptoms after removal from exposure is in keeping with the natural history of asthma induced by other chemicals including isocyanates.

The maleic anhydride exposure
levels on Jackson and Jones's graph are interesting, although they are semiquantitative. The relation of the haemolytic anaemia with maleic anhydride was based on his known sensitisation to maleic anhydride and the temporal relation between exposure and disease. The graph does seem to show an increase in exposure to maleic anhydride at least before the second episode of haemolysis. It is true that the tests we performed looking for in vitro haemolysis in the presence of maleic anhydride were negative but the laboratory concerned had never done these tests before. Our original paper also noted that maleic anhydride was used chemically to modify erythrocyte membrane proteins to produce a foreign protein. This provides a mechanism by which maleic anhydride may cause haemolysis.

The findings of Jackson and Jones of positive antibodies in workers without symptoms is interesting. In the only study we are aware of with this type of result, the positive RAST cut off was obtained by calculating isotope binding three standard deviations above the mean of that in 20 samples of umbilical cord blood. This could be anywhere between 0.4% and 1.4%. By contrast our worker's maleic anhydride RAST binding ranged from 10.5% to 15.6% which is of a completely different order and less likely just to reflect exposure.

One of the unusual features of the reported case is the persistence of IgE antibodies after occupational exposure ceased. The concentrations decreased, however, at the rate seen for other acid anhydrides and are consistent with removal from exposure with some re-exposure. We point out that environmental exposures do not only occur when the worker is at home, and it is likely that our worker went closer to the factory than 8 km on occasion after leaving work. Source of re-exposure other than factory emissions include contact with contaminated workmates outside the workplace induced by antigen on their hair and clothing, for example.

We were aware of disagreement with our patient's account of his symptoms but Jackson was kept informed throughout the preparation of the paper and our patient was shown Jackson's comments and allowed to modify his account before publications.

We understand Jackson and Jones' concerns that haemolytic anaemia is not incorrectly associated with maleic anhydride. If a clinician subsequently has to deal with an autoimmune haemolytic anaemia in a worker who is exposed to maleic anhydride, however, we believe that our report serves to point out that workplace exposure should be added to the list of possible aetiologies.

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NOTICES

An international congress on occupational health will be held in Nice, France 26 September–1 October 1993.

This is a major event in the life of the International Commission and to a wider extent in the world of occupational health and the industrial environment.

For a brochure and registration form (reduced prices for replies received before 1 May 1993) contact: CO24 France, Les Miroirs Cedex 27, 92096 Paris La Defense. Telephone 33 (1) 47.62.33.70; Fax 33 (1) 47.62.31.53.

An intensive course in occupational epidemiology will be held in Wermelskirchen, Germany, 23–28 May 1993.

The intensive course in occupational epidemiology (ICOE) is a five day instructional course in the concepts, approaches, methods, analysis, and interpretation of occupational epidemiological research. It is specifically designed to provide occupational physicians and other interested health professionals with the essential background necessary for critically reading and interpreting published epidemiological research, designing basic epidemiological studies, and assembling and analysing data pertaining to the health of worker populations. Course topics will be the epidemiological perspective, history of occupational epidemiology, occupational study design options, basic analytical techniques, preven-