gastric and thyroid autoimmunity shown in the family studies of Doniach and Roitt (1966), and that our patient illustrates the results of such an inheritance from each of his parents.

We would like to thank Dr. Deborah Doniach, of the Middlesex Hospital Medical School, London, and Dr. George McDonald, of the Royal Infirmary, Glasgow, for assistance with the antibody studies in this family.

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Sudden Death in a Young Asthmatic

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British Medical Journal, 1969, 2, 29–30

Summary: A 14-year-old boy with severe asthma was treated with prednisone and disodium cromoglycate with considerable subjective improvement, though there was persistent airways obstruction. After several weeks' freedom from symptoms he died in a severe attack of nocturnal asthma. Necropsy findings suggested that hypersecretion had been occurring in the medium-sized airways for several days before death.

Recently there has been great concern over the increasing mortality from asthma, particularly in children aged 10–14 years (Speizer *et al.*, 1968a, 1968b).

This case report concerns a 14-year-old boy who died suddenly in a severe attack of asthma. Before his death he was taking prednisone and disodium cromoglycate. Both forms of treatment were being taken regularly until a few hours before the terminal episode.

Case Report

A boy aged 14 was referred to the Brompton Hospital on 29 January 1968. He had had eczema in infancy and had begun to have asthma at the age of 2 years. For five months previous to his referral asthma had become increasingly severe and he had been absent from school for long periods. At first he had obtained temporary relief from two six-day courses of betamethasone, but later cough and wheezing had become continuous and he was using his pressurized metered aerosol (orciprenaline) very frequently, requiring a refill canister once a week. For the previous two weeks he had taken betamethasone (1.5 mg. a day).

He was a cheerful and apparently well-adjusted boy. He was thin and rather small for his age. There was a dorsal kyphosis and a prominent sternum, and the chest was fixed in a position of hyperinflation. Expiratory and inspiratory rhonchi were present throughout both lungs. Peak expiratory flow (P.E.F.) was unrecordable.

The results of relevant investigations on admission were: absolute eosinophil count 100/cu. mm. Sputum: no eosinophils and no pathogenic organisms. Skin tests: grass pollens positive, feathers weak positive, control and all other tests negative. Chest x-ray film: no abnormality. Forced expiratory volume in one second/forced vital capacity: 1.60/2.90 litres.

Other lung function tests (predicted normal values in parentheses) showed: vital capacity 3.10 litres (3.30 litres). Functional residual

capacity 2.53 litres (1.45 litres). Total lung capacity 4.53 litres (4.28 litres). Diffusing capacity (steady-state method): at rest 21.9, on exercise 34.8 ml. CO/min./Hg.

On corticotrophin gel (40 units daily) his subsequent progress was good. His P.E.F. continued to rise, reaching a maximum of 450 litres/min. five days after admission (predicted normal P.E.F., 400–450 litres/min.). By the time of his discharge on 15 February betamethasone had been withdrawn and he had been taught to give himself injections of corticotrophin (40 units) twice a week. His parents thought that he was better than he had been for many years. However, three weeks later (11 March) his condition had deteriorated and the frequency of corticotrophin injections was increased to 40 units daily. On the next day he had a severe attack of asthma, during which he lost consciousness and had an epileptiform convulsion. He was treated at another hospital with oxygen and intravenous aminophylline and was allowed home after a few hours.

A week later it was decided to stop corticotrophin and to substitute prednisone 30 mg. a day. Within two days he was considerably better and was able to return to school. Prednisone was continued with gradual reduction in dose, and on 8 April he was taking 10 mg. a day. He was well and able to play football and needed to use his pressurized aerosol only once or twice in 24 hours. Nevertheless, no further improvement had occurred in the level of P.E.F., and it was decided to treat him with disodium cromoglycate. Careful instructions about its use and purpose were given and he was told to inhale one Spincap four times per day. This produced further symptomatic improvement, and therefore on 29 April prednisone was reduced to 7.5 mg. a day.

On 7 May he appeared to be perfectly well, and that evening he played football vigorously. About midnight he awoke coughing and wheezing. After two inhalations of orciprenaline from his metered aerosol he seemed to obtain complete relief and fell asleep. This sequence of events was repeated three hours later. Two hours later he woke up and was very distressed. His father, who had stayed in his room, noticed that his colour became blue, but that he did not appear to be wheezing. The boy coughed once or twice and then suddenly collapsed and became unconscious. No convulsion occurred. During the ambulance journey cardiac arrest occurred, and external massage and artificial respiration were given. Despite this, however, he was dead when he arrived at another hospital, about 40 minutes after the onset of the final attack.

At necropsy the lungs were greatly distended and the bronchi congested, all being plugged with tenacious mucus. The right ventricle of the heart was dilated and hypertrophied. A slice of one lobe was taken to Professor Lynne Reid for histological examination. In the large airways there were numerous eosinophils and the basement membrane was thickened. In some areas there were numerous distended goblet cells, and some of the submucosal mucus glands were found to be hypertrophied. The medium airways were

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blocked with mucus, which showed a laminar arrangement. The smaller airways at the level of the terminal bronchioles were mostly clear of secretion, and the alveoli contained no mucus. In some alveoli, however, particularly those surrounding the small airways, there were numerous macrophages which contained P.A.S.-positive material. The connective tissue septa of the lungs were oedematous.

Discussion

We have no reason to doubt the accuracy of the father's observations, and hence an excessive inhalation of orciprenaline cannot be incriminated as a contributory cause of death.

Speizer *et al.* (1968b) found that in 30% of patients on corticosteroids at the time of their death the dose had been maintained at a moderate or low level or was being reduced. They suggested that these patients may have had adrenal suppression as a result of previous steroid therapy, and that the maintenance dose of steroids, which they were receiving at the onset of the terminal episode, had been insufficient to give protection against the stress of the disease.

Grant (1968) thought it probable that in some cases in which death had occurred unexpectedly there had been a failure on the part of the patient himself or his relatives or his doctor to appreciate the significance of warning signs. In the present case the only warning that occurred was the two short-lasting episodes of asthma which awoke the boy from his sleep.

In retrospect it seems probable that the boy was in a vulnerable state for several weeks before his death. Despite his lack of symptoms during most of the time when he was receiving

prednisone, there was a considerable degree of persistent airways obstruction. All the measurements of P.E.F. recorded during that period were much lower than those which he had achieved when he was in hospital (see Chart).

The laminar arrangement of mucus which was found post-mortem in the medium-sized airways suggests that hypersecretion had been occurring over a period of several days before death. The P.A.S.-positive material which was present in some macrophages was probably mucus that had been removed from the alveoli, into which it had been aspirated during the previous episode of status asthmaticus two months earlier. It is possible that during that episode many airways became blocked by mucus or exudate, and the persistence of such blockage would explain the relatively poor improvement in P.E.F. which followed the resumption of corticosteroids. The suddenness of death probably accounts for the absence of mucus within the alveoli themselves: aspiration of mucus into alveoli is commonly found in fatal cases of asthma (Reid, personal communication, 1969).

For the last four weeks of his life this boy was taking disodium cromoglycate. Detailed histological examination showed no evidence of any harmful effects that might have been caused by this drug. There is therefore no reason to suppose that disodium cromoglycate was in any way directly contributory to this boy's death. Nevertheless, it seems possible that the subjective relief which he obtained from disodium cromoglycate may have further obscured a dangerous situation. Altounyan and Howell (1969) have pointed out that some patients derive great subjective benefit from disodium cromoglycate in the absence of any improvement in tests of ventilatory function. In the case of this boy disodium cromoglycate may have deprived him of warning symptoms at a time when he was especially vulnerable owing to the persistent airways obstruction and also because the dose of prednisone had been reduced to a level that gave only marginal protection against allergic or other challenge.

We wish to thank Dr. Richard Pearce, who performed the post-mortem examination, and Professor Lynne Reid, who carried out the histological examination of the lungs.

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Treatment and serial measurements of P.E.F. from January to May 1968. A=admission, D=discharge.