Down's Syndrome, Hypothyroidism, and Diabetes Mellitus

SIR,—The observation that some diseases are associated with chromosomal disorders—for example, congenital heart disease and Hirschsprung's disease in Down's syndrome—has cast some light on their aetiology. It therefore seems right to draw attention to other, similar associations. There have been two previous reports of patients with Down's syndrome who have developed both hypothyroidism and diabetes mellitus[1 2] and I now report a third.

The patient, a girl, was the sixth child of a 35-year-old mother. She was diagnosed at birth as having Down's syndrome and this was later confirmed by chromosome analysis (trisomy-21). Her growth and development were slow but she was cherished by her family and during her fifth year she began to attend a junior training centre. However, at the age of 5 years it was noticed that she appeared to be hypothyroid. Her height and weight were well below the third centile and she had thin, dry hair, a pale puffy face, and cold hands. Her bone age then was 1 year 3 months (Greulich and Pyle's method), her Thyopac-3 ratio was 1·24, which is in the hypothyroid range, and her serum thyroid-stimulating hormone (TSH) level 480 μU/ml. She was therefore started on treatment with thyroxine and this resulted in a definite growth spurt. When she was 6½ years old she was admitted to hospital as an emergency in diabetic coma, her blood sugar being 1,800 mg/100 ml and her blood urea 325 mg/100 ml. She died the following day and necropsy was not performed.

This patient's history suggests two things. The first is that it now seems unlikely that the association of hypothyroidism, diabetes mellitus, and Down's syndrome should have occurred by chance. The second, confirmed by her raised serum TSH level, is that hypothyroidism in Down's syndrome, an association that has been reported on several occasions,[3] is of thyroid rather than pituitary origin.—I am, etc.,

J. M. PARKIN

Children's Clinic,
Royal Victoria Infirmary,
Newcastle upon Tyne

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Threshold for Oxygen Pneumonitis

SIR,—In a recent paper by Sevitt[1] it is suggested that it may be dangerous to expose patients to higher concentrations of oxygen than 40% on the grounds that this may give rise to focal or diffuse pneumonitis. It has been appreciated for many years that oxygen therapy carries certain hazards but it is generally considered that to cause pulmonary damage the concentration must be appreciably greater than 40%. Because of the extensive use of oxygen therapy in wards and special units we believe it is important to review the evidence presented in the paper before accepting the opinions expressed, with all their implications.

Out of 21 patients surveyed, 18 had sustained pulmonary trauma either directly or indirectly (chest injuries, 11; fat embolism, 3; possible fat embolism, 2; smoke inhalation, 2). Three patients did not have primary pulmonary damage but had sustained head injuries, and no mention is made of the level of consciousness of these (or other) patients.

The values quoted for the concentrations of oxygen breathed by the patients were spread over a very wide range and were measured in only six cases, and no blood gas tensions are given. One adult patient is stated to have been maintained inside an oxygen tent at 40% oxygen (measured) for eight days. This is almost impossible to achieve unless the tent was never opened for feeding or other nursing or therapeutic procedures, because each time it is opened the tent atmosphere returns to that of ambient air and, because of its large capaciy, there is a considerable delay before the desired oxygen concentration can be achieved after each such manoeuvre.

At no point in the paper is reference made to other methods of treatment or to coincidental clinical disturbances such as sepsis, cardiac failure, or renal failure. There are several reasons why these omissions may be significant in this context. It has been known for many years that respiratory failure is an important cause of the morbidity and mortality of patients suffering from trauma, haemorrhage, or systemic infection, and the syndrome of post-traumatic respiratory insufficiency ("shock lung") is of great interest. There are many possible causes for this condition which include bronchopneumonia, fat embolism, pulmonary oedema, pulmonary contusion, endotoxinaemia,[2] disseminated intravascular coagulation,[3] and pulmonary microemboli originating in transfused blood or plasma or in damaged tissues.[4] Oxygen toxicity may also be incriminated, but it is essential to exclude these other conditions before attributing this clinical syndrome exclusively to oxygen toxicity.

Finally, it must be recognized that the lungs can respond in only a limited way to a variety of physical, infective, or metabolic insults and that the histological changes described in the paper may be seen in conditions as varied as recurrent infection, pulmonary burns, renal failure, and paraquat poisoning.

We believe that this paper draws attention to the potential hazards of oxygen therapy but that the findings may be interpreted in another way.—We are, etc.,

J. A. J. FERRIS
J. C. STODDART

Royal Victoria Infirmary,
Newcastle upon Tyne

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2 Dowd, J., and Jenkins, L. C., *Canadian Anaesthetists Society*, 1972, **19**, 309.
3 Cuevas, P., *et al.*, *Archives of Surgery*, 1972, **104**, 319.
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*** Drs. Ferris and Stoddart sent a copy of their letter to Dr. Sevitt, whose reply we print below.—ED., *B.M.J.*

SIR,—My paper is criticized by Drs. Ferris and Stoddart on a number of grounds, though they admit that high concentrations of inspired oxygen for a sufficient time can cause serious hypoxaemia from pulmonary damage. My purpose was to try to ascertain the threshold oxygen concentrations and periods of exposure which can produce lung damage in man. This important aspect is very difficult to establish in man from clinical observations alone as so many factors are involved, and it has not apparently been investigated in animals. A combined clinicopathological approach was required.

A group of patients who reached necropsy after various exposures to oxygen therapy were studied, some of whom died with and others without hypoxaemia. Essential details of the arterial P_{O_2} values are given in the paper if Drs. Ferris and Stoddart will read it again. For histological assessment the definite criteria of pulmonary hyaline membranes and proliferative pneumonitis were used and the findings divided into diffuse and focal pneumonitis. These were correlated with the presence or absence of hypoxaemia, radiological lung changes, and other matters, and from the overall findings it was concluded that breathing 40% oxygen for a sufficient time seems to be the threshold for dangerous lung effects. Higher concentrations were often associated with fatal hypoxaemic pneumonitis and lower concentrations with only focal or no lung damage. Of course the histological changes described are not specific to oxygen poisoning, as I pointed out, but known causes like paraquat and busulphan poisoning, topical mafenide therapy, and viral afflictions were not relevant. The pneumonitis found was regarded as due to oxygen damage in the clinical settings described because the lungs of many other injured and burned subjects were examined and the changes were not found in the absence of oxygen therapy. Local proliferative foci were otherwise seen only related to local causes like edges of infarcts or foci of organizing pneumonia, and such cases were eliminated from the series. The suggestion, apparently supported by Drs. Ferris and Stoddart, that pneumonitis associated with hyaline membranes can develop de novo in severely injured patients as part of the obscure condition referred to as "shock lung" was considered, investigated, and not confirmed. Pneumonitis appeared only when oxygen had been given.

My critics state that "it is generally considered that to cause pulmonary damage the concentration [of oxygen] must be appreciably greater than 40%". What evidence have they for this statement? By comparing the pulmonary effects of concentrations ranging from 30% to 100% oxygen given for various periods I found that 40% was about the threshold. This approximation has been confirmed in two more recent patients given 40% oxygen for days. One died with severe hypoxaemia and diffuse bilateral pneumonitis, while the other recovered.

With great respect to Drs. Ferris and Stoddart, may I add that their letter reflects a kind of rearguard action of the curious opposition in certain circles during recent years to the concept that too much oxygen can damage the lungs?—I am, etc.,

S. SEVITT

Pathology Department,
Birmingham Accident Hospital,
Birmingham

Other Systemic Effects of Eye Drops

SIR,—The interesting report by Mr. M. K. Wang and Dr. J. R. Tatane (9 March, p. 453) of hallucinations in their 6-year-old patient which followed the instillation of one drop to each eye of 1% cyclopentolate followed by one drop of 0·25% hyoscine