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.,

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¹ Daniels, D. M., and Simon, J. L., *Journal of Pediatrics*, 1968, 72, 697.

² Litman, N. N., *Journal of Pediatrics*, 1968, 73, 798.

³ Hayles, A. B., Hinrichs, W. L., and Tauxe, W. N., *Pediatrics*, 1965, 36, 608.

Threshold for Oxygen Pneumonitis

SIR,—In a recent paper by Sevitt¹ 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 capacity, 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, endotoxaemia,² disseminated intravascular coagulation,³ and pulmonary micro-emboli 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.,

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J. C. STODDART

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¹ Sevitt, S., *Journal of Clinical Pathology*, 1974, 27, 21.

² Dowd, J., and Jenkins, L. C., *Canadian Anaesthetists Society*, 1972, 19, 309.

³ Cuevas, P., et al., *Archives of Surgery*, 1972, 104, 319.

⁴ Stoddart, J. C., and Wardle, E. N., *British Journal of Anaesthesia*, 1974, in press.

⁵ Blaisdell, F. W., and Stallone, R. J., *Surgery, Gynecology and Obstetrics*, 1970, 130, 15.

** 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 clinico-pathological 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 PO_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 affections 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.,

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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

concludes with the statement that "the remarkable feature, however, is that a sufficient amount of drugs could be absorbed from a few drops of dilute solution to produce such dramatic effects." On the contrary, it is evidently not appreciated that the "few drops of dilute solution" do, in fact, contain a substantial dose of each drug. The volume of a single drop from an eye dropper bottle of a type in common use is about 0.06 ml so that two drops (one to each eye) of 1% cyclopentolate solution contains 1.2 mg and two drops of 0.25% hyoscine solution contains 0.3 mg. Thus under the conditions described a significant amount of each drug was potentially available for absorption into the general circulation particularly since the normal *adult* systemic dose of hyoscine hydrobromide is 0.3-0.6 mg; cyclopentolate is not normally administered systemically.

Following the application of a drug to the eye the rate and amount of it absorbed not only locally but also systemically depends upon a variety of factors including the dose employed. It is known that hallucinations can be produced by cyclopentolate¹ and hyoscine² and in view of the ophthalmological doses normally employed in children what seems even more remarkable is the fact that this adverse reaction is not seen more frequently, particularly when mydriatics are used in combination. These points reinforce the important comments made in your leading article on the effect of eye drops on babies' blood pressure (5 January, p. 2).—I am, etc.,

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¹ Binkhorst, R. D., et al., *American Journal of Ophthalmology*, 1963, **55**, 1243.

² Goodman, L. S., and Gilman, A., *The Pharmacological Basis of Therapeutics*, 4th edn., p. 528. New York, Macmillan, 1970.

Unsuspected Cytomegalic Mononucleosis

SIR,—In your leading article (2 March, p. 340) it is implied that polyneuritis is the rarest complication of acquired cytomegalovirus infection. In our experience it has been the most common one, and nine cases have already been reported from Britain.¹ In two of the last five cases of cytomegalovirus infection in previously healthy young adults diagnosed by us polyneuritis was probably present.

The first patient, a girl of 18, had a three-week history of sore throat, paraesthesiae, progressive weakness, headache, and joint pains. She was found to have normal sensation and co-ordination but gross weakness of the legs and absent reflexes in all four limbs. She had a raised E.S.R. with a relative lymphocytosis. One month after the onset of symptoms cytomegalovirus was isolated from the throat swab and a specimen of urine, and her serum showed a complement-fixing antibody titre to cytomegalovirus of $> 1/160$ with specific IgA and IgM antibodies shown by immunofluorescence. Her antibody titre to Epstein-Barr virus in this specimen was $< 1/5$ and her Paul-Bunnell titre $< 1/20$, though the Monosticon test with neat serum was positive. Treatment with corticotrophin for six weeks led to a slow but complete recovery after three months of convalescence.

The second patient was a woman of 28

with an illness resembling glandular fever which was most remarkable for the intensity of the headache, photophobia, and joint pains associated with marked difficulty in walking and which was followed intermittent pyrexia for some weeks and depression for several months. She also developed paraesthesiae of the hands and arms 2½ months after the onset. During the first month of her illness her complement fixation titre to cytomegalovirus rose from $< 1/5$ to $\geq 1/160$ and specific IgA and IgM antibodies appeared and were still detectable four months later. A year after the onset of this infection she was still suffering intermittently from photophobia and paraesthesiae in one hand. Her Paul-Bunnell test was negative.—We are, etc.,

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J. L. TAYLOR

Birch Hill Hospital,
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¹ *Quarterly Journal of Medicine*, 1971, **40**, 435.

Metoclopramide and Cardiac Arrhythmia

SIR,—Metoclopramide is considered to be free from side effects in adults,¹ though extrapyramidal signs have been described in psychiatric patients to whom very high doses were administered.² Dystonic reactions such as torticollis, oculogyric crises, and trismus have also been observed in children receiving this drug.³ We here report a case of multifocal supraventricular extrasystoles appearing after a single intramuscular injection of metoclopramide on two occasions.

A 55-year-old woman was admitted because of vomiting. There was no previous history of rhythm disturbances. The heart sounds, electrocardiogram, and serum electrolyte levels were normal. Metoclopramide 10 mg was injected intramuscularly; 15 minutes later the patient complained of palpitations, her pulse became irregular, and in her electrocardiogram multifocal supraventricular extrasystoles were noted. Antiarrhythmic drugs were not administered and the rhythm returned to normal after one hour. Readministration of the same dose of metoclopramide on the next day was followed by the same rhythm disturbance.

Metoclopramide does not produce adverse effects on the cardiovascular system in dogs.⁴ To our knowledge this is the first reported case of arrhythmia due to metoclopramide in man.—We are, etc.,

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Petah Tiqva, Israel

¹ James, W. B., and Hume, R., *Gut*, 1968, **9**, 203.

² Borenstein, P., and Bles, G., *Therapie*, 1965, **20**, 975.

³ Casteels-Van Daele, M., et al., *Archives of Disease in Childhood*, 1970, **45**, 130.

⁴ Malméjac, J., and Laville, C., *Pathologie et Biologie*, 1964, **12**, 1074.

Temporarily Dependent Patients in General Practice

SIR,—Dr. K. B. Thomas's article (30 March, p. 625) on the declared outcome of "untreated" patients in general practice was most interesting, but seemed to me to contain some unjustified assumptions. They

include: (1) that if the general practitioner cannot diagnose a disease, physical or psychological, the patient "is not ill"; (2) that if such a patient got better without treatment, this confirms that he was not ill; and (3) that a visit to a general practitioner is equivalent to becoming dependent.

Dr. Thomas fails to take into account the fact that a decision to consult a doctor may often be a complex one and may finally be taken as a result of pressures from "lay" advisers.^{1,2} To equate the end result of an often complex interaction with becoming temporarily dependent seems an oversimplification, at least.

A vast mass of symptoms in the community do not ever reach a doctor—no doubt if they did, Dr. Thomas would find even more patients whom he could not diagnose. Whether or not a doctor is consulted, fortunately for mankind and particularly for the medical profession most of these do get better in spite of, because of, or without treatment. And of course "getting better" is ambiguous, connoting equally "improved" or "returned to normal." And even if there was no notable change for the better after a medical consultation, many patients would be too kind to report to their doctor that he had totally failed.

Anecdotally one hears all too often the story of the patient with a serious or lethal disease whose doctor could find nothing wrong with him at first. It is useful to be reminded that this is not always due to an individual doctor's incompetence, but in fact reflects the state of the art and science of early diagnosis; and it is cheering to be reminded by Dr. Thomas that usually the results of our inabilities are shielded from us by the healing powers of nature.—I am, etc.,

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Department of Community Medicine,
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¹ Robinson, D., *The Process of Becoming Ill*. London, Routledge and Kegan Paul, 1971.

² Freidson, E., *Patients' Views of Medical Practice*. New York, Russell Sage Foundation, 1961.

SIR,—I think that Dr. K. B. Thomas's article (30 March, p. 625) is important because it re-emphasizes the large number of "undiagnosed" patients visiting general practice surgeries who should not, therefore, receive pharmacologically active preparations.

However, it is misleading in his discussion to say that "most of this group of patients who received no treatment other than contact with their doctor improved" when earlier it is stated that "a few received nothing at all, and most received a placebo." The conclusion that "patients are often made to feel better with no treatment other than contact with [the doctor]" cannot be drawn from these results as equally it could be said that they improved because they were given "something"—that is, the placebo.—I am, etc.,

RICHARD J. ROBERTSON

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Inversion of the Appendix

SIR,—I believe that this method of "removing" the appendix was described at the end of the last century, and from time to time has gained popularity, particularly with