fall in responsiveness has not been related to the unloaded ventilatory response. Our results suggest that the fall in ventilatory response to CO₂ produced by loading is partly dependent on the initial responsiveness, with unresponsive individuals showing the greatest percentage fall in slope.

These observations are in accord with the hypothesis that the premorbid CO₂ responsiveness modifies a patient's adaptation to airways obstruction. A patient who when healthy is poorly responsive to CO₂ might therefore be expected to underventilate more readily when airways obstruction develops and thus CO₂ retention will be facilitated. A similar line of argument has been postulated to explain the origins of chronic mountain sickness in terms of previous insensitivity to hypoxia (Severinghaus, Bainton, and Carcelen, 1966). A corollary of this argument might be that unresponsive individuals tolerate greater rises in PCO₂, but we failed to observe any correlation between the maximum PCO₂ achieved during rebreathing and the unloaded CO₂ responsiveness.

The resistances used were high and noticeably reduced FEV₁ (R₁ approximately halved FEV₁ and R₂ reduced it by 75%). They were the same for inspiration and expiration and were used throughout the respiratory cycle as it seems likely that CO₂ retention can be produced by obstruction either during expiration or during inspiration (Clark, 1970).

We thought it also desirable to examine the relation between CO₂ responsiveness, added airways resistance, and CO₂ excretion. The effect of added respiratory loads is not easy to interpret in terms of alveolar CO₂ tension (Pope, Holloway, and Campbell, 1968; Freedman and Campbell, 1970) and it was thought undesirable to examine changes in arterial blood gas tensions. As well as raising PCO₂ in arterial blood and alveolar air an inability to maintain normal CO₂ excretion might also be seen as a transient fall in respiratory exchange ratio ($\dot{V}_{CO_2}/\dot{V}_{O_2}$) which would return to normal values once a new steady state has been achieved in response to the sustained added load. We therefore examined the immediate changes in respiratory exchange ratio while breathing through a resistance and were

able to show impaired CO₂ excretion which appeared to bear a relation to the initial CO₂ responsiveness. This relation was consistent with that observed in terms of changes in responsiveness and lends support to the idea that relatively unresponsive subjects are more liable to retain CO₂ in the presence of acute airways obstruction.

The idea that CO₂ retention is not explicable purely in terms of the mechanical abnormality is well established in chronic airways obstruction (Lane and Howell, 1970) and obesity (Lourenco, 1969) and the discrepancies observed have largely been explained in terms of an abnormal CO₂ responsiveness. This explanation still leaves the problem of deciding whether the abnormal CO₂ responsiveness is a primary or a secondary phenomenon. Our results support the hypothesis that part of the explanation for CO₂ retention may lie in the constitutional CO₂ responsiveness of the patient who develops airways obstruction.

Requests for reprints should be sent to Dr. T. J. H. Clark.

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MEDICAL MEMORANDA

Cerebrotendinous Xanthomatosis

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Tendon xanthomas are a reliable indication of hypercholesterolaemia and warn of an increased risk of coronary heart disease (Beaumont *et al.*, 1963). The case reported here is an exception to the rule. The patient's tendon xanthomas were associated with mental defect and a barely raised serum cholesterol. This combination is rare and apparently has not been described in the British medical literature.

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Case Report

A white woman aged 47 had been in the Alexandra Institution (for mentally defective people) from the age of 25. At that time her I.Q. was assessed as 38 though according to her family she appeared to have been mentally normal until she was about 14. Her birth was said to have been normal. A visit to the family in the Ceres district of the Cape province provided the additional information that she was probably retarded from early childhood. Though she attended a farm school and learnt to write her name she could never read. She was the sixth of nine children. Her parents were first cousins and so were her father's parents. One of her brothers, who was dead, had been mentally defective and lumps had been present on his elbows and knees. Her father had died of myocardial infarction. Her mother suffered from rheumatoid arthritis.

Fatty tumours on both Achilles tendons were excised in 1952. Similar tumours appeared in both patellar tendons and were excised in 1967. Histologically they were xanthomas. The Achilles tendon xanthomas recurred and extensive excisions were performed in 1969. Histological examination showed sheets of xanthoma cells, large cholesterol spaces, foreign body giant cells, and fibrosis. The same year bilateral dense nuclear and cortical cataracts were found and the right lens was extracted.

On examination she was found to have a moderately severe mental defect; she could speak some English and Afrikaans and was left eye and asteroid hyalitis in the right eye. The right fundus was normal. There were scars in front of both knees and behind

both ankles where xanthomas had been removed, with some loss of superficial parts of the Achilles tendons. A xanthoma had recurred at the lower end of the left patellar tendon. There were no xanthomas elsewhere. The lower end of the right radius was thickened. Other physical appearances were normal. Examination of the nervous system showed a tremor of the outstretched left hand and mild inco-ordination of all limbs, more pronounced on the left. All deep reflexes were brisk, with bilateral finger flexion; plantar reflexes were normal. Sensation appeared normal and gait was unsteady. On lumbar puncture C.S.F. was slightly hazy with 60 mg of protein and no cells.

X-ray examination showed a Smith-Petersen nail in the right femoral neck and an old fracture at the lower end of the right radius. All the bones were somewhat porotic. Lung fields were within normal limits. Results of blood counts and standard biochemical tests were normal. Fasting serum cholesterol levels were 295, 288, and 247 mg/100 ml (method of Abell *et al.*, 1952), and triglyceride was 160 mg/100 ml. Paper electrophoresis showed mildly increased betalipoproteins and prebetalipoproteins. Betalipoprotein cholesterol was 202 mg/100 ml. E.C.G. showed slight sag of the ST segment in lateral leads.

Comment

The combination of mental defect, possibly of late onset, with cerebellar ataxia, increased deep reflexes, juvenile cataracts, and massive tendon xanthomas with minimally raised serum cholesterol is characteristic of cerebrotendinous xanthomatosis. This condition was first noted by van Bogaert in 1937 (Phillipart and van Bogaert, 1969). About eight cases have been described since then (Schimstock *et al.*, 1968).

The dementia can present in late childhood or in adult life. Serum cholesterol levels have been normal or transiently

raised. Most of the deaths have been from gradual pseudobulbar paralysis, and one man aged 58 died of myocardial infarction. At necropsy there have been granulomatous lesions and demyelination in the cerebellar white matter lateral to the dentate nuclei, with less severe similar lesions elsewhere in the central nervous system. The disease appears to be inherited as a Mendelian recessive, as in the present case. Accumulation of free and esterified cholestanol—that is, cholesterol without its 5, 6 double bond—is the specific biochemical lesion in the nervous system (Menkes *et al.*, 1968; Phillipart and van Bogaert, 1969), where the saturated sterol makes up a quarter to half of the total sterols. In tendon xanthomas and in serum, however, the percentage of cholestanol is much lower and may (Phillipart and van Bogaert, 1969) or may not (Menkes *et al.*, 1968) be of diagnostic value during life.

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Prolonged Coma after Tetanus

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Tetanus still carries a considerable morbidity and mortality (Weinberg, 1964), particularly when it is severe and occurs in older subjects (Kerr *et al.*, 1968). We report the case of an elderly woman with severe tetanus successfully treated with pancuronium (a short-acting curare-like drug) and massive doses of diazepam. There were no serious side effects but she remained unconscious for 12 days after treatment was stopped.

Case History

A 72-year-old spinster with no relevant past medical history collapsed in her garden on the evening of 25 October 1970. She was found the next morning somewhat confused, dirty, and with multiple lacerations affecting particularly the knees and the right big toe. She was admitted to the surgical ward of another hospital where the wounds were cleaned and excised and the right big toe was amputated.

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Eight days later she developed trismus. She was given penicillin and tetanus antitoxin before transfer to this hospital. On arrival, about three hours after the onset of trismus, she was also noted to have stiffness of the neck muscles but apart from obesity (weight 79 kg) appeared fit for her age and was mentally fully alert. She was given more antitoxin (100,000 units intravenously) and started on a course of parenteral penicillin. Shortly afterwards she felt nauseated, vomited once, and had a major spasm with respiratory arrest. She was immediately intubated and an emergency tracheostomy was performed. Her wounds were opened and all suspicious tissue was excised. Tetanus bacilli were cultured from debris removed from the right foot.

After tracheostomy she was ventilated artificially, paralyzed with pancuronium, and heavily sedated with diazepam. On the first day she received 220 mg of diazepam intravenously, on the second day 815 mg, and overall a mean dose of 70 mg daily. This dosage did not produce any recognizable side effects and her blood pressure remained stable throughout (110-130/80 mm Hg). During the first two or three days her condition deteriorated and she developed generalized rigidity, with severe spasms as often as every 20 minutes and minor spasms each time she was touched, despite 50-80 mg of pancuronium daily.

Her further course was complicated by bronchospasm, bronchopneumonia, urinary infection, mild renal and cardiac failure, and a deep vein thrombosis. These were treated appropriately.

Twenty-one days after her admission the major spasms had stopped, though she remained rigid and had spasms if touched. The pancuronium was stopped and she was maintained on diazepam. She was weaned off the ventilator gradually until she was breathing completely unaided nine days later. Diazepam had been stopped 28 days after the onset of trismus. She remained rigid and unconscious for a further 12 days though capable of spontaneous respiration through the tracheostomy, and only then made some response to commands such as "open your mouth" or "move your fingers." The muscular stiffness persisted and passive movements of the limbs were made difficult by pronounced cog-wheel rigidity. There was little evidence of any further improvement in mental function