became euthyroid, calcium could be retained on a restricted intake even in the presence of the parathyroid adenoma. Wayne (1960) suggests that the hypercalciuria of thyrotoxicosis is due partly to an increased glomerular filtration rate and partly to hypercalcaemia, and in the present case the initial creatinine clearance was greatly elevated but fell to normal on antithyroid therapy. Creatinine clearance may be a limited index of glomerular filtration rate in thyrotoxicosis, but the change is significant.

Hyperuricaemia in hyperparathyroidism has only recently been recognized. Mintz *et al.* (1961) recorded four cases and Bywaters *et al.* (1963) found 11. Scott *et al.* (1964) report acute gouty arthritis in 5 of these 11, postulating that the hyperuricaemia is due to calcium deposition in the renal tubules. In the present case the initial serum uric acid was only slightly elevated, but after antithyroid treatment it rose to 10.4 mg./100 ml. without producing arthritic symptoms. This rise suggests that the defect in uric-acid metabolism was partially compensated by the coexisting thyrotoxicosis, possibly on the basis of the increased glomerular filtration rate. The fall in the uric acid level after surgery suggests that the renal tubular defect was still reversible despite the six-year history of renal colic.

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Muscle Necrosis and Calcification in Acute Renal Failure Due to Barbiturate Intoxication

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The occurrence of muscle necrosis has already been reported in acute renal failure due to barbiturate intoxication and carbon monoxide poisoning (Hedinger, 1948; Touzé and Thierry, 1952; Loughridge *et al.*, 1958; Jackson *et al.*, 1959; Seddon, 1964) and in chronic alcoholism (Fahlgren *et al.*, 1957; Hed *et al.*, 1962).

In the following case the patient exhibited muscle necrosis and calcification during the course of severe acute renal failure due to barbiturate intoxication.

CASE REPORT

A man aged 35 was admitted to hospital on 24 November 1963 having taken an overdose of pentobarbitone. He had been found, deeply comatose, lying on his right side some 17 hours after taking the drug. The systolic blood-pressure was 80 mm. Hg, and his extremities were cold and cyanosed. The upper part of his right arm appeared to be swollen.

Twenty-four hours after ingestion of the drug the blood barbiturate level was 4.2 mg./100 ml. A policy of forced diuresis was adopted, and his systolic pressure was maintained in the region of 100-120 by means of metaraminol. His urine volume, however, fell progressively, and by the fourth day the blood urea had risen to 398 mg./100 ml. Haemodialysis was carried out on four occasions at intervals of two to three days, during which time consciousness slowly returned. The swelling persisted in the right shoulder and dilated veins were visible over the deltoid prominence. Radiography revealed no abnormality in the right shoulder, and the left shoulder was in every respect normal.

During the next few days gross swelling developed in both hips, extending into the thighs, particularly on the right. Bullous lesions were noted over the medial femoral condyles, the right lateral malleolus, the contiguous aspects of both feet, and the right deltoid.

It was thought that necrosis affecting the right deltoid and the muscles of the hips might be responsible for the severe uraemia and might explain the swelling and tenderness over these areas. A biopsy of the right deltoid muscle provided histological evidence of organizing focal necrosis. It seemed most likely that a similar change had occurred in the gluteal muscles, though a biopsy of this site was not carried out. Radiographs of the right shoulder and hips taken three weeks after admission showed extensive calcification of the gluteal muscles on both sides. This persisted unchanged for two months, but by the end of three months it had virtually disappeared. No calcification was observed in the right deltoid. Unfortunately blood calcium levels were not investigated during the oliguric stage when the calcification was occurring, since its development was not foreseen. The radiological appearances of the bones were normal throughout. Renal biopsy confirmed the presence of acute tubular necrosis.

The subsequent course was stormy. A typical diuretic phase occurred, complicated by septicaemia and severe pulmonary oedema with marked cardiac enlargement and a persistent tachycardia. These problems were eventually overcome, and by the end of December all the biochemical findings had returned to normal; his further progress was uneventful.

MUSCLE NECROSIS

The clinical features of muscle necrosis in this patient are similar to those described by others in barbiturate intoxication. Possible aetiological factors in this instance were pressure, hypotension, and hypoxia, together with any direct effect that barbiturates may have on muscle and its vasculature.

The localizing effect of pressure has been stressed in most of the reported cases of non-traumatic muscle necrosis (Mautner, 1955; Fahlgren *et al.*, 1957; Loughridge *et al.*, 1958; Jackson *et al.*, 1959; Hed *et al.*, 1962).

Although pressure may account for the deltoid lesion, bilateral gluteal calcification could not have been produced by pressure with the patient lying on his right side.

The possibility that muscle necrosis may result from changes in the muscle vasculature has to be considered. Little work has been done on the direct effect of barbiturates on muscle blood-flow, but it is possible that an element of stagnant hypoxia is added to that due to central respiratory depression. It is conceivable that arteriovenous shunts may exist, short-circuiting blood across the muscle capillary beds. However, the work of Folkow *et al.* (1961) on consecutive sections of muscle vessels, and of Piiper and Rosell (1961) with wax spheres, suggests that this type of shunt does not exist in skeletal muscle.

Muscle necrosis and the bullous skin lesions sometimes seen in barbiturate intoxication (as in the present case) could be related. Beveridge and Lawson (1965) thought the bullous lesions might be due to a primary toxic action of the barbiturate.

It might prove possible to obtain advance confirmation of muscle necrosis from the urine amino-acid-excretion pattern. Bowden and Goyer (1962) noted the production of massive taurinuria in rats which had developed muscle necrosis as a result of treatment by the antimalarial plasmocid, a powerful myotoxin. The possibility that muscle necrosis in the human may produce similar changes in the urine is worth bearing in mind.

CALCIFICATION

The infusion of calcium in patients with hyperkalaemia led to the observation that in those involving muscle damage the amount of calcium necessary to maintain a constant plasma level was greater than in similar cases without muscle damage. This led Meroney *et al.* (1957) to perform an experiment in which it was shown that the calcium content of traumatized muscle in dogs was doubled within six hours, whereas in nephrectomized dogs the content was increased tenfold. Full understanding of calcium deposition awaits further elucidation of intracellular and extracellular ionic relations in acute renal failure.

The radiological changes in soft-tissue calcification have been reviewed by Hilbish and Bartter (1962). Muscular calcification or ossification has been reported to follow the

convulsions of tetanus, in anterior poliomyelitis (Costello and Brown, 1951), in cases of severe burns, and in patients who have been stuporous for long periods (Johnson, 1957). In these instances the calcification was assumed to be due to immobility combined with systemic disturbances in protein and electrolyte metabolism. The term "atypical myositis ossificans" was suggested by Johnson (1957). The distribution of calcium in these cases was not related to pressure but rather, it was surmised, to minor trauma occurring during coma or anaesthesia. The radiological appearances in the present case in no way resemble those seen either in progressive or in traumatic myositis ossificans, or indeed in any of the para-articular ossifications reported above. The fact that it resolved spontaneously puts it into a different category, almost certainly related to the metabolic changes associated with recovery from renal failure.

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A Second Family Demonstrating the Homozygote for the Fluoride-resistant Pseudocholinesterase Variant

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A 46-year-old man suffering from recurrent agitated depression was admitted to the psychiatric wards for a second course of electric convulsion therapy. A course had been given in 1963, and after the first treatment he developed severe muscular pains affecting the limbs, chest, and abdomen, which persisted for nearly a week. No prolongation of the normal apnoeic period was noted, but thereafter Flaxedil (gallamine triethiodide) was substituted for the suxamethonium used on the first occasion as muscle relaxant, and the symptoms did not recur. In view of his unusual reaction to the first treatment, when he was admitted for the second course of therapy it was decided to assay his serum pseudocholinesterase level. The initial studies suggested that he was likely to be homozygous for the

unusual fluoride-resistant form of the enzyme, and in order to check these findings samples of blood were obtained from his parents, sister, and his only child, a son.

METHODS AND RESULTS

The serum pseudocholinesterase levels were determined by the micromanometric method of Ammon (1933), dibucaine (cinchocaine) numbers by the method of Kalow and Genest (1957), and fluoride numbers by the method of Harris and Whittaker (1961).

The results of the enzyme assays and inhibition studies on the three generations of the family are shown in the Table.

DISCUSSION

The ability of the short-acting muscle relaxant suxamethonium to induce prolonged apnoea in a minority of patients with a low level of serum pseudocholinesterase (acylcholine acylhydrolase, Enzyme Commission No. 3.1.1.8)