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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J. G. CLARK, M.B., F.R.C.S.,
Surgical Registrar, Royal Infirmary, Edinburgh. Late Senior House Officer, Renal Unit, Royal Infirmary, Edinburgh.
M. D. SUMERLING, B.SC., M.B., CH.B., M.R.C.P., F.F.R.,
Consultant Radiologist, Royal Infirmary, Edinburgh.

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

*Brit. med. J.*, 1966, **2**, 215–216

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

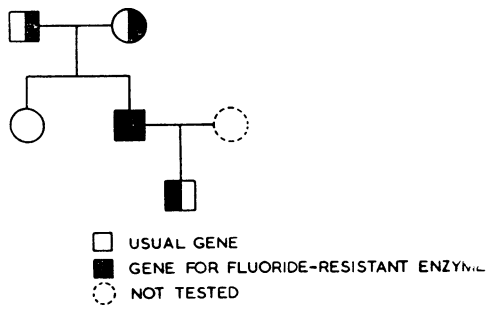
The ability of the short-acting muscle relaxant suxamethonium to induce prolonged apnoea in a minority of patients with a low level of serum pseudocholinesterase (acylcholine acylhydrolase, Enzyme Commission No. 3.1.1.8)

*Serum Pseudocholinesterase Levels and Inhibition Studies on a Family Exhibiting the Harris and Whittaker Variant*

| Individual | Age | Pseudo-cholinesterase Level (I.U.) | Dibucaine Number | Fluoride Number | Presumed Genotype |
|---|---|---|---|---|---|
| Father .. | 87 | 5·3 | 76 | 53 | Heterozygote for usual and fluoride-resistant gene |
| Mother .. | 79 | 4·1 | 73 | 51 | " " |
| Propositus | 46 | 4·4 | 68 | 35 | Homozygote " for fluoride-resistant gene |
| Sister .. | 57 | 5·8 | 81 | 69 | Usual homozygote |
| Son of propositus | 21 | 4·2 | 72 | 54 | Heterozygote for usual and fluoride-resistant gene |
| Usual range | | 2·2–5·5 | 77–83 | 57–68 | |

is now well known (Bourne, Collier, and Somers, 1952; Evans, Gray, Lehmann, and Silk, 1952). That different symptoms, such as those seen in the patient concerned in this study, also occur is not well known. Investigation has led to the suggestion that low enzyme levels could be genetically determined (Lehmann and Ryan, 1956; Lehmann, Patston, and Ryan, 1958; Kaufman, Lehmann, and Silk, 1960). Kalow and Genest (1957), and Kalow and Staron (1957) demonstrated that inheritance of a low level of enzyme activity was associated with an atypical cholinesterase.

Four variants have now been described, the most common of which differs from the normal form in being less active against a wide range of substrates and more resistant to many cholinesterase inhibitors. Dibucaine is the inhibitor used to distinguish this variant (D) from the usual type (Kalow and Davies, 1958; Davies, Marton, and Kalow, 1960). A second variant of less certain type has been described by Lehmann, Silk, Harris, and Whittaker (1960). A third variant (Liddell, Lehmann, and Silk, 1962), in which the serum betrays no pseudocholinesterase activity, has been designated the "silent" gene. Goedde, Gehring, and Hofmann (1965) reported that




A second family with a homozygote for the fluoride-resistant pseudocholinesterase gene.

they could find very slight activity in the serum of a homozygote for the "silent" gene. The fourth variant (F) (Harris and Whittaker, 1961, 1962) is inhibited less strongly than the normal gene, not only by the quaternary ammonium compound dibucaine but also by sodium fluoride, the percentage inhibition by dibucaine (dibucaine number DN) being slightly lower and the percentage inhibition by fluoride (fluoride number FN) being much lower than is found with the usual type. Of the four families described by Liddell, Lehmann, and Davies (1963) one appeared to contain two homozygotes for the fluoride-resistant gene (Lehmann, Liddell, Blackwell, O'Connor, and Daws, 1963). No other cases of a homozygote for this gene are known to us to be recorded in the literature.

Fortunately, three generations of the family discussed in this paper were available for study (see Chart), and the results provide further evidence for the existence of the allelomorphic variant first described by Harris and Whittaker (1961, 1962). The studies of Liddell *et al.* (1963) on the first probable homozygotes for the fluoride-resistant pseudocholinesterase gene provided results remarkably similar to those of the present study. The propositus and the other homozygote in that family respectively had pseudocholinesterase levels of 3.3 and 2.5 I.U., dibucaine numbers of 67 and 64, and fluoride numbers of 34 and 35. The patient in the present study had a higher pseudocholinesterase level (4.4 I.U.) and similar inhibition figures, DN 68 and FN 35. The heterozygotes of the earlier study had pseudocholinesterase levels of 4.1–5.3 I.U., dibucaine numbers of 72–76, and fluoride numbers of 52–55—that is, again a closely similar inhibition pattern to the heterozygotes of the family reported here. The members of the first family who were homozygous for the normal gene naturally gave results similar to the sister in this study (DN 78–82 and FN 61–64), the DN for the sister being 81 and the FN 69.

Thus this English family resembles to a degree the Cypriot family described by Lehmann *et al.* (1963), and presents additional evidence of the Harris and Whittaker variant being allelomorphic for the usual pseudocholinesterase gene.

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P. D. GRIFFITHS,* M.D., B.SC., M.C.PATH.,
Consultant Pathologist, Herts and Essex General Hospital, Bishop's Stortford.
DAPHNE DAVIES, B.SC., PH.D.,
Biochemist, M.R.C. Abnormal Haemoglobin Research Unit, University Department of Biochemistry, Cambridge.
H. LEHMANN, M.D., SC.D., F.R.C.P., F.C.PATH., F.R.I.C.,
University Biochemist, Addenbrooke's Hospital; Director M.R.C. Abnormal Haemoglobin Research Unit, University Department of Biochemistry, Cambridge.

* Present address: Department of Clinical Chemistry, Royal Infirmary, Dundee.

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