pigs, however, thiopentone appeared to give protection against the initiation of the syndrome by either halothane alone or the halothane/suxamethonium combination. In South African pigs halothane can initiate the syndrome in the presence of neuromuscular block produced by tubocurarine (Harrison, 1971), and we were able to produce the syndrome in our known reactors given this relaxant, although in these animals the course of the reaction was modified. We agree (Hall *et al.*, 1966), however, that non-depolarizing relaxants have no therapeutic effect once the syndrome is established. Our results also confirm the findings of Harrison *et al.* (1969) that adrenaline will not produce muscle contracture in susceptible animals, supporting the contention that in our pigs, and possibly in the South African pigs, environmental stress fails to produce the syndrome.

It is also interesting to note that while the American workers quoted by Ellis (1971) claimed that magnesium ions protect their pigs from developing malignant hyperthermia Harrison *et al.* (1969) found that magnesium sulphate completely lacked therapeutic effect.

In 1970 Kalow suggested that malignant hyperthermia in man could be a syndrome resulting from more than one defect, and the conflicting findings in pigs suggest that the same may be true for the porcine syndrome. Thus although we believe that the pig is proving to be a valuable experimental animal for the

study of this condition great caution must be exercised in transposing results from one breed or strain of pigs to another breed or strain, or to man.

Our investigations are far from complete but this early report is prompted by the lack of any specific treatment for the syndrome based on a knowledge of its pathogenesis. We believe that at present immediate cooling coupled with sodium bicarbonate administration provides the best chance of success when dealing with the type of syndrome seen in our pigs. We were unable to show any indication for the administration of procaine hydrochloride, which was reported by Harrison (1971) to be a promising line of treatment for his animals.

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MEDICAL MEMORANDA

Hypertension and Oedema Complicating Pregnancy in Addison's Disease

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Pregnancy associated with Addison's disease is rarely complicated by pre-eclamptic toxæmia. Toxaemia has been reported in Addison's disease (Cohen, 1948; Langford, 1965), after bilateral adrenalectomy (Moses *et al.*, 1959; Barber *et al.*, 1966), while in the case reported by Strickland and Sode (1967) the patient had recurrent oedema only.

Case Report

The patient had had uncomplicated full-term pregnancies in 1953 and 1958. In 1960 she had a severe episode of "gastroenteritis" with admission to an infectious diseases hospital and requiring intravenous fluid and steroid therapy for hypovolaemic shock. In May 1961 she presented at Manchester Royal Infirmary with weakness, loss of weight, exertional breathlessness, loss of libido, and scanty but regular menstruation. She was found to have increased generalized pigmentation, especially in palmar creases and buccal mucosa, with diminished body hair. Blood pressure was 90/65 mm Hg. Urinary 17-oxosteroid excretion was 1.2 mg/24

hr, and 17-oxogenic steroids never exceeded 1 mg/24 hr and did not rise after corticotrophin gel 60 units daily for three days. Only 40% of a water load was excreted in four hours. Abdominal x-ray examination did not show adrenal calcification.

She remained well on replacement therapy and in early 1969 was receiving 12.5 mg of cortisone acetate twice daily and 9 α -fluorohydrocortisone acetate 0.1 mg daily. Routine serum electrolyte measurements were normal and lying and standing blood pressure was regularly 110/80 mm Hg.

She was first seen in her third pregnancy at 16 weeks' gestation on 29 May 1969, when the uterus corresponded to dates. (Last menstrual period 7 February, expected date of confinement 14 November.) She was seen again at 19 weeks' gestation and the uterine size was that of a 24-week pregnancy. From that time the uterine size did not accord with dates. Fetal movements had been felt for two weeks. Blood pressure was 110/80 mm Hg and her weight was 49 kg. At 22 weeks the size of the uterus corresponded to a gestation of 34 weeks, with pronounced hydramnios and with an increase in weight to 54 kg. Blood pressure had risen to 125/75 mm Hg, but urine analysis was normal. Abdominal x-ray examination confirmed a normal twin pregnancy with radiological maturity corresponding with dates.

Five days later, after admission, her weight had risen to 57.8 kg and the blood pressure to 140/100 mm Hg. Severe oedema had developed but urine analysis remained normal. Frusemide 40 mg was added to her treatment without improvement. Three days later the fludrocortisone was discontinued and within 24 hours the blood pressure had fallen to 120/85 mm Hg. This level was maintained for six days, when fludrocortisone was reinstituted. Serum electrolytes remained normal (see Chart). Within 24 hours the blood pressure rose and four days later had reached 140/100 mm Hg. Once more the fludrocortisone was discontinued with resultant fall in blood pressure to 120/80 mm Hg. Abdominal girth had reached 102.5 cm and weight was constant at 57.6 kg.

The clinical state remained virtually unchanged for 11 days, but at that time the serum sodium level fell to 131 mEq/l. and postural hypotension occurred for the first time. Fludrocortisone was started again but the blood pressure remained constant at 110/70 mm Hg though the serum electrolytes returned to normal and the postural hypotension disappeared. The Kober chromogen level fell from the average level of 5 mg/24 hr to 1.5 mg/24 hr

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and six days later twin macerated stillborn male fetuses weighing 392 g and 646 g were delivered spontaneously during the 28th week of pregnancy.

Comment

The unusual feature of this case was the noticeable sensitivity to fluorohydrocortisone. It is known that in normal pregnancy desoxycorticosterone acetate does not produce oedema and hypertension (Assali *et al.*, 1953) and in our own experience postadrenalectomy patients require little alteration in maintenance therapy during pregnancy. In this patient when the fluorohydrocortisone was discontinued the oedema became less and tension of the hydramnios decreased, suggesting that there was a distinct loss of sodium and water. The blood pressure did not fall below 120/80 mm Hg, however, and the serum sodium did not fall below normal until the final sudden drop when signs of hypovolaemia and postural hypotension rapidly ensued. In retrospect it is likely that fetal death precipitated

loss of sodium and water. It appeared that while the fetuses were alive a second process was promoting sodium retention and increased blood pressure, rendering the patient more sensitive to mineralocorticoid therapy. She was able to maintain blood pressure and serum sodium levels without fludrocortisone, and the sudden appearance of hypovolaemia and hypotension was associated with fetal death.

We have hesitated to call this condition pre-eclamptic toxæmia in the absence of proteinuria, though by definition the development of oedema and hypertension in pregnancy, which may occur early in twin pregnancy, could be so described. The pronounced effect of the mineralocorticoid is unlikely to have resulted from the changes in protein binding of the steroid seen in pregnancy in respect of cortisol (Doe *et al.*, 1969; O'Connell and Welsh, 1969; Rosenthal *et al.*, 1969), as 9 α -fluorohydrocortisone appears to be much less avidly bound (Daughaday, 1958). The cortisone may have had an increased mineralocorticoid effect, but the dose was low, although the oestrogen levels of pregnancy would also contribute. Further, it is recognized that endogenous steroids produced by the fetus are transferred to the maternal circulation (Harkness *et al.*, 1966).

It is unlikely that 9 α -fluorohydrocortisone was a major factor in producing the oedema and hypertension but it cannot be doubted that the condition was grossly exacerbated by its use and that improvement occurred when it was discontinued. When fetal death occurred the need for mineralocorticoid therapy returned rapidly. The nature of the "toxæmic" process is not clear, and whether it was related to placental steroid or other hormone production is not known.

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