(2) when there is a raised concentration of lactate dehydrogenase. The latter would cause changes in optical density before the addition of the 3-hydroxybutyrate dehydrogenase, and is due to the conversion of plasma pyruvate to lactate with accompanying utilization of NADH. In this situation perchloric acid extraction would have to be performed.

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Successful use of Oral Diazoxide in the Treatment of Severe Toxaemia of Pregnancy

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Summary

Treatment with oral diazoxide for periods of 4 to 10 weeks in hospital allowed adequate control of hypertension with continuation of fetal growth in four patients with severe toxaemia. Two were insulin-dependent diabetics and one of these suffered from renal failure. In all patients albuminuria diminished markedly, while the fluid retention was controlled with frusemide. Three pregnancies were successfully terminated by lower segment caesarean section and in the remaining case vaginal delivery resulted in the birth of a healthy baby. Control of blood sugars presented no problems in the diabetic patients. Only minimal adjustments of insulin dosage were required. One of the non-diabetic patients developed mild hyperglycaemia which responded to tolbutamide. The babies, ranging in age from 5 to 12 months, have continued to thrive.

Introduction

The successful management of severe toxaemia of pregnancy demands the control of the raised blood pressure as well as the maintenance of adequate placental perfusion and renal function. Conventional therapy achieves only the first of these objectives. Intravenous diazoxide has been reported by Finnerty (1962) to produce favourable results in toxaemia of pregnancy. We wish to report the successful use of oral diazoxide in four patients presenting with severe toxaemia of pregnancy (see Table).

Diazoxide Dosage, Associated Maternal Condition, and Age of Babies

Case No.	Diazoxide	Age of Infant	Associated Maternal Medical Condition
1	100 mg q.d.s.	12 months	Diabetes mellitus. Kimmelstiel-Wilson syndrome
2	250 mg q.d.s.	6 „	Diabetes mellitus
3	100 mg t.d.s.	8 „	Infertile 9 years
4	200 mg q.d.s.	5 „	

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Case 1

A 24-year old insulin-dependent diabetic of 12 years' standing was first documented as having albuminuria with mild hypertension eight years previously. She presented to this hospital in June 1970 in the third month of her second pregnancy with a blood pressure of 130/90 mm Hg, proteinuria, but without oedema or retinopathy. Her blood urea was 28 mg/100 ml. In July 1970 at 17 weeks her blood urea had risen to 54 mg/100 ml, and the serum creatinine was 2·0 mg/100 ml.

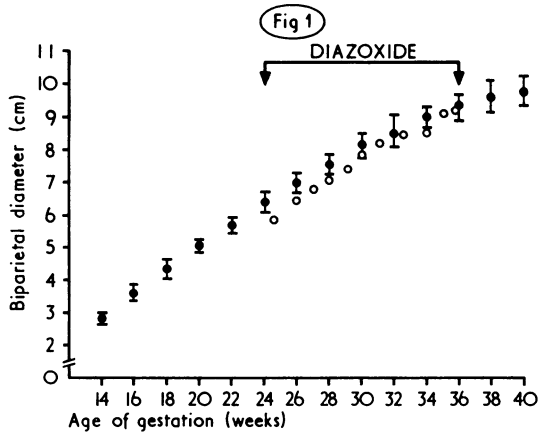
Early in August she was readmitted with a haemoglobin of 9·0 g/100 ml, for a total dose infusion of Imferon. This was ineffective, however, and by the end of September, when her haemoglobin had fallen to 7·2 g/100 ml, she was transfused with 2 pints (1,140 ml) of packed cells. Later in August her final admission was precipitated by progressive hypertension (135/100), increasing albuminuria, and the development of dependent oedema. Retinal haemorrhages were observed for the first time.

She was treated with heavy sedation and strict bed rest, but did not improve. In September, at the twenty-sixth week of pregnancy, her blood pressure was 180/110, and she had generalized oedema, hydramnios, a raised jugular venous pressure, and hepatomegaly. There were fresh haemorrhages in both fundi. The blood urea was 54 mg/100 ml, the urinary protein leak was 4 g per 24 hours and the serum albumin was 2·9g/100 ml. Termination of pregnancy was considered but a trial of diazoxide was held to be a justifiable alternative. Treatment with oral diazoxide 50 mg three times a day increasing to 100 mg four times a day was begun and her blood pressure fell to 110/70 and was maintained near that level for the remaining 10 weeks of her pregnancy. Her urinary protein leak fell to 0·5 to 1 g a day. The fluid retention was overcome by the use of up to 200 mg of frusemide daily but there was no consistent effect on the hydramnios.

The diabetic control was maintained with twice-daily injections of a mixture of soluble and isophane insulin. After the introduction of diazoxide an increase from 4 to 8 units total daily dose of insulin was required. The only discomfort the patient suffered during the remainder of her pregnancy was the well-known side effect of nausea and occasional vomiting. The persistent hydramnios may well have been a

contributory factor. Fetal progress was satisfactory as assessed by serial ultrasonic scanning—that is, scans of the biparietal diameter (Fig. 1)—and repeated urinary oestriol estimations (Fig. 2).

Maternal renal function was monitored by repeated urea and creatinine estimations and the calculation of 24-hour endogenous creatinine clearances (see Fig. 3). In mid-November when the pregnancy was at 36 weeks by dates and the fetal scans suggested a maturity of 35 + weeks the pregnancy was terminated by elective lower segment caesarean section. The diazoxide was discontinued 12 hours before operation. A normal looking 5-lb (2,270 g) male infant was delivered. The child required only minimal resuscitation and continued to thrive. The mother made a satisfactory recovery and was discharged 12 days later. At that time her blood pressure was 180/100 on no treatment and the serum creatinine had fallen to 1·0 mg/100 ml. Four weeks from delivery the blood pressure was 170/90. A year later her blood pressure was 180/90, on 0·5 g of chlorothiazide per day.



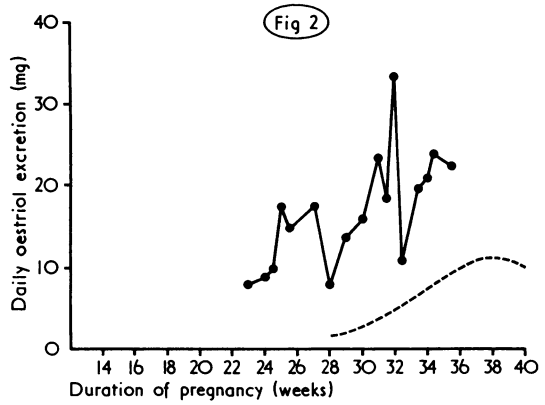


FIG. 1—Case 1. Ultrasonic scans of the fetal biparietal diameters (open circles). The normal growth curve is shown by the closed circles, the vertical bars denote ± 2 S.D. FIG. 2—Case 1. 24-hour maternal urinary oestriol excretion. The broken line denotes the lower limit of acceptable urinary oestriol excretion.

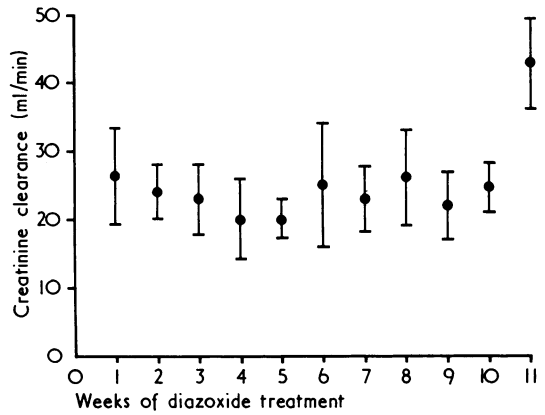


FIG. 3—Case 1. Average weekly creatinine clearances based on continuous urine collections (the vertical bars denote ± S.D.).

Case 2

A 27-year-old insulin-dependent diabetic of 13 years' standing developed marked albuminuria with generalized oedema and blood pressure up to 160/110 in her third pregnancy at 32 weeks despite bed rest and sedation. Her renal function was normal. She was treated with oral diazoxide and frusemide for a period of four weeks. During this time the albuminuria fell to a trace, her blood pressure was controlled, and the oedema resolved. Serial ultrasonic scans showed satisfactory growth and confirmed the clinical improvement of the moderate hydramnios. At 36 weeks she was successfully delivered of a live female infant by elective lower segment caesarean section. The child made good progress. The maternal insulin requirements were increased slightly by the diazoxide treatment.

Case 3

A 34-year-old primigravida at 32 weeks developed hypertension, albuminuria with oedema, and was admitted to hospital. She was treated with sedation, bed rest, diuretics, and methyldopa without effect. Oral diazoxide was started during the thirty-third week of pregnancy when her blood pressure was 160/115. Her blood pressure fell to normal and the albuminuria decreased. Fetal growth remained satisfactory until 36 weeks when on the basis of failure to observe further fetal growth the pregnancy was terminated by elective lower segment caesarean section. A live boy who was delivered continued to do well. The mother's blood sugar remained normal until one week before delivery when mild hyperglycaemia not accompanied by ketosis was easily controlled by tolbutamide. Diazoxide and tolbutamide were discontinued at delivery and there was no recurrence of either hypertension or hyperglycaemia.

Case 4

A 28-year-old multigravida developed generalized oedema, hypertension, and a trace of albuminuria in her fourth pregnancy at 28 weeks' gestation (according to her dates). Her blood pressure rose to 165/120 despite bed rest in hospital. At 29 weeks treatment with diazoxide and frusemide was begun. The blood pressure was easily controlled, the oedema and albuminuria disappeared. Fetal growth was satisfactory during the five-week period of treatment. Labour was induced at 34 weeks by dates but at 38 weeks' maturity by ultrasonic scan and a live female infant weighing 3,600 g was born by normal vaginal delivery. The infant made good progress and the mother's blood pressure did not relapse when the diazoxide was tailed off. All the maternal blood sugars were normal during the period of diazoxide treatment.

Discussion

The fetal prognosis is very poor when hypertension complicates pregnancy and proves resistant to therapy (Chesley and Annitto, 1947; Landesman *et al.*, 1955). The increasing maternal risk in this situation limits the time for which the pregnancy can be allowed to continue. In our patients fetal death from prematurity was highly likely if the pregnancies could not be safely prolonged. Intravenous diazoxide has been advocated by Finnerty (1962) and has been found by him to be effective in the control of toxaemic hypertension. The need for repeated intravenous injections has limited the duration and hence utility of such therapy. Our experience with the long-term use of oral diazoxide in the treatment of hypertension complicated by renal damage (Pohl and Thurston, 1971) suggests the use of this therapy in uncontrollable hypertension of pregnancy.

Diazoxide is a non-diuretic bendrothiadiazine derivative with pronounced hypotensive properties (Finnerty, 1968) and tends to produce hyperglycaemia by inhibition of pancreatic insulin release (Dollery, 1962; Loubatières *et al.*, 1966). This hyperglycaemia has been shown to respond to oral sulphonylurea therapy (Wolff, 1964). Diazoxide lowers hypertensive blood pressures by producing generalized vasodilation (Nayler *et al.*, 1968; Schmitt *et al.*, 1968). This would be expected to benefit the maternal renal blood flow and placental perfusion, and this is

important since vasoconstriction would seem to be one of the mechanisms by which toxaemia of pregnancy may produce damage (Morris *et al.*, 1955; Dixon *et al.*, 1963). It proved easy to maintain complete blood pressure control in our patients with oral diazoxide and prolongation of pregnancy by up to 10 weeks was achieved. The diminution or abolition of albuminuria which occurred in all four patients suggests at least an amelioration of the toxaemic process and this suggestion is further supported by the normal fetal growth which took place during the period of treatment.

The successful conclusion of pregnancy in Case 1 despite the presence of considerable renal failure may well have been related to the increased renal blood flow which diazoxide is known to produce.

The only important side effect of oral diazoxide therapy that was encountered was sodium and fluid retention (Pohl *et al.*, 1972) which responded satisfactorily to frusemide. The need for twice-daily blood sugar estimations made it necessary for the patients to stay in hospital for the remainder of pregnancy. Only Case 3 developed hyperglycaemia during the last week of diazoxide treatment. Although this was easily controlled by oral tolbutamide the cessation of fetal growth at this stage suggests that treatment with insulin would have been better. The reported effect of diazoxide in diabetics is variable (Graber *et al.*, 1966; Black, 1968). In our two diabetic patients (Cases 1 and 2) the effect was minimal and only trivial increases of insulin dosage were required. In the absence of hyperglycaemia oral diazoxide therapy cannot have impaired fetal endogenous insulin production since glucose tolerance tests on the newborn babies were normal (Milner, and Chouksey, 1972).

The successful and yet fairly easy management of four cases of severe hypertension in pregnancy resistant to other therapy suggests to us that oral diazoxide deserves a trial in the management of this condition, but it is important to see and treat these patients early. We have seen other patients with much more severe hypertension, possibly antedating pregnancy, in which there has been an appreciable fetal mortality.

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MEDICAL MEMORANDA

Isolation of Herpes Virus from Erythema Multiforme

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Herpes virus has occasionally been isolated from lesions of erytheme multiforme (Shelley, 1967; Söltz-Szöts, 1969) but the presence of the virus has never been fully explained, nor has opportunist secondary infection or contamination been excluded in some of these cases.

We report a case in which severe herpes simplex cervicitis was followed by an eruption of erythema multiforme type. Herpes virus was readily grown from the skin lesions, which were also remarkable for the intensity of their inflammatory reaction.

Case Report

A 27-year-old woman developed dyspareunia, a thick vaginal discharge, and, two weeks later, dragging lower abdominal pain and dysuria. On admission she was acutely ill with a temperature of 40°C. The lower abdomen was extremely tender and a tender, bulky uterus was palpated per vaginam. So distressing was this manoeuvre that the cervix could not be adequately inspected. Acute salpingitis with pelvic peritonitis was diagnosed. Shortly afterwards vesicles characteristic of herpes simplex appeared on the vulva and herpes cervicitis became the presumptive diagnosis.

Soon after admission she developed an extensive and somewhat bizarre eruption involving the face, scalp, limbs, trunk, and perineal regions, consisting of discrete, fixed plaques up to 10 cm in diameter. No further lesions appeared but those present soon became covered by malodorous adherent crusts, some as thick as 2 cm, from under which serum continued to exude.

She was initially treated with ampicillin and trimethoprim-sulphamethoxazole (Septrin) (Fig. 1). Five weeks later, however, although the fever had diminished and the gynaecological condition improved the skin disorder was still causing her much distress (Fig. 2). Various topical medicaments (gentamicin, betamethasone valerate, idoxuridine, eusol) had been of little benefit. She was then given prednisolone up to 80 mg daily. Activity of the lesions persisted for two more weeks, when suddenly and for no apparent reason the crusts became dry and began to separate. Some 15 weeks after admission to hospital the lesions had almost healed (Fig. 3). Although there was hepatic tenderness in the acute stage of the illness general physical examination throughout had elicited no other abnormalities.

INVESTIGATIONS

The haemopoietic system including bone marrow was normal apart from relative lymphopenia. The E.S.R. which was initially over 100 mm/hr, fell to normal before her discharge. Biopsy of a lesion showed tissue grossly distorted by the acuteness of the inflammatory process. Neither balloon cells nor inclusion bodies indicative of virus infection nor a perivascular infiltrate suggestive of erythema multiforme were seen.

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