[10] Spence, J H, *British Medical Journal*, 1937, 2, 1169.
[11] Morton, J H, and Schwartz, S I, in *Progress in Gynaecology*, ed J V Meigs, and S H Sturgis, vol 4. London, Heinemann, 1963.
[12] Antony, A T, and Wallace, J T, *New York State Journal of Medicine*, 1962, 62, 3462.
[13] Millar, D R, and Øvlisen, B, *Acta Obstetricia et Gynecologica Scandinavica*, 1966, 46, 254.
[14] Thompson, J W, and Le Blanc, L J, *American Journal of Surgery*, 1945, 67, 123.
[15] Anderson, G W, *American Journal of Obstetrics and Gynecology*, 1942, 43, 883.
[16] McGarvey, R N, Freeman, J J, and Fox, P F, *American Journal of Obstetrics and Gynecology*, 1952, 64, 655.
[17] Jones, P F, McEwan, A B, and Bernard, R M, *Lancet*, 1969, 2, 350.
[18] Fielding, J F, and Cooke, W T, *British Medical Journal*, 1970, 2, 76.
[19] De Dombal, F T, Burton, I L, and Goligher, J C, *British Medical Journal*, 1972, 3, 550.
[20] Blair, J S G, and Allen, N, *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1962, 69, 648.
[21] Boreham, P F, and Soltau, D H K, *British Medical Journal*, 1970, 2, 541.
[22] Jones, R L, and Soltau, D H K, *Journal of Obstetrics and Gynaecology of the British Empire*, 1958, 65, 811.
[23] Williams, D L, and Davis, D R, *Southern Surgeon*, 1946, 12, 342.
[24] Berk, J E, Smith, B H, and Akrawi, M M, *American Journal of Gastroenterology*, 1971, 56, 216.
[25] Friley, M D, and Douglas, G, *American Surgeon*, 1972, 38, 314.
[26] Beischer, N A, *et al*, *Australian and New Zealand Journal of Obstetrics and Gynaecology*, 1971, 11, 208.

Occasional Survey

Bromocriptine treatment of female infertility: report of 13 pregnancies

M O THORNER, G M BESSER, ANN JONES, JANET DACIE, A E JONES

British Medical Journal, 1975, 4, 694-697

Summary

Thirteen pregnancies occurred in 12 women who were treated with bromocriptine for infertility. Pretreatment prolactin levels were recorded in 11 patients and were normal in three. Five patients had suspected pituitary tumours, and they received irradiation to prevent swelling of the pituitary and the consequent visual field defects caused by the pressure of the swollen gland on the optic nerve. Ten of the 13 pregnancies have come to term, and all the babies were normal. When a patient with a pituitary tumour developed a visual field defect in the 38th week of pregnancy labour was induced and the defect disappeared after delivery. No multiple pregnancies occurred and there were no major complications.

Introduction

Raised prolactin levels are usually associated with hypogonadism whether or not there is associated galactorrhoea. Bromocriptine (2 brom-α-ergocryptine, CB 154), a long-acting dopamine receptor agonist, lowers prolactin levels and this is associated with a return of normal ovarian function, even in patients with pituitary tumours.[1-7] An unresolved problem exists in patients with pituitary tumours, however, When gonadotrophin treatment is used to induce pregnancy in such patients there is a risk that visual field defects may develop from the swelling of the pituitary and consequent optic nerve compression.[8-12] This complication occurs during gonadotrophin therapy in at least 3% of cases.[11] Presumably the same risk exists in any patient with a pituitary tumour who becomes pregnant.

We report here our experience of 13 pregnancies in 12 infertile women who were treated with bromocriptine and discuss the management policy adopted in these patients, with particular reference to those suspected of having pituitary tumours.

Departments of Endocrinology, Chemical Pathology, Diagnostic Radiology, and Radiotherapy, St Bartholomew's Hospital, London EC1A 7BE

M O THORNER, MB, MRCP, lecturer in medicine
G M BESSER, MD, FRCP, professor of endocrinology
ANN JONES, BSC, AIMLT, research assistant
JANET DACIE, MRCP, FRCR, consultant radiologist
A E JONES, MD, FRCR, professor of radiotherapy

Patients and methods

The 12 patients were first seen at St Bartholomew's Hospital between 1969 and 1974 with infertility (see table). Seven of them (cases 1-3, 6, 8, 10, and 12) have been referred to elsewhere.[5] No patient had evidence of hepatic or renal disease and none had taken any drugs likely to raise prolactin levels except for an oral contraceptive in cases 8 and 9. None had evidence of acromegaly and all patients had normal thyroid function; only one patient (case 1) had a reduced ACTH reserve, and three (cases 2, 3, and 4) had a reduced growth hormone (GH) reserve when tested with insulin-induced hypoglycaemia. The patients' husbands were all normal on seminal analysis.

Galactorrhoea had been present in 10 of the 12 patients for eight to 96 months, and in one other patient it was found only on expression of the breast during routine examination.

Menstrual history—Nine patients had had amenorrhoea for six months to 16 years before treatment. Three patients had had irregular periods for four to five years before treatment. Infertility had been present for six months to 12 years.

Oestrogen-progestogen treatment—In two patients amenorrhoea supervened after combined oestrogen-progestogen treatment had been prescribed for irregular menstruation; in one spontaneous galactorrhoea appeared during this treatment, but it was not present in the other.

Normal prolactin levels—Three patients with normal serum prolactin levels were given bromocriptine; one had galactorrhoea in association with amenorrhoea, another had galactorrhoea with irregular periods, and the third had developed amenorrhoea after combined oestrogen-progestogen treatment and we thought it worthwhile to try bromocriptine as this often promotes fertility in patients who develop amenorrhoea, hyperprolactinaemia, and galactorrhoea after taking oral contraceptives.

MEASUREMENTS AND TESTS

All basal blood samples were taken between 9 and 10 am, at which time all dynamic function tests were started.

Assays—Serum prolactin, luteinising hormone (LH), follicle-stimulating hormone (FSH), thyrotrophin (TSH), and GH were measured by radioimmunoassay.[13-15] The normal ranges in women are: prolactin <4-18 μg/l (MRC standard 71/222); LH in the follicular phase of the cycle 1·4-9·8 U/l (MRC standard 68/40, 77 IU/ampoule); and FSH in the follicular phase 0·8-3·2 U/l (MRC standard 69/104, 10 IU/ampoule). Standards for TSH were MRC standard 69/38 and for GH 1st International Reference Preparation. Plasma cortisol was measured fluorometrically.[16]

Tests—Intravenous gonadotrophin-releasing hormone (Gn-RH) tests (100 μg)[17 18] and thyrotorophin-releasing hormone (TRH) tests (200 μg)[13 19] were performed in 10 of the 12 patients, with LH and FSH being measured after the former test and TSH after the latter. Insulin tolerance tests[13] were performed in 11 of the 12 patients. Intravenous soluble insulin 0·15 U/kg was given, and blood sugar, GH, and cortisol were measured.

Management policy

All patients were carefully screened for evidence of pituitary tumours. Our level of suspicion of a tumour was high as micro-adenomata that secrete prolactin tend to be peripheral and small, and often the only evidence of their presence is slight asymmetry of the pituitary fossa on skull *x*-ray films, giving the appearance of a double floor on the lateral skull film or a slight dip in the floor on the postero-anterior view.[20] The five patients with such appearances or with obvious abnormalities of the pituitary fossa or abnormal insulin tolerance, Gn-RH, or TRH test results were then submitted to air encephalography to exclude any suprasellar extension of a tumour. If they wanted to become pregnant and had any evidence of a pituitary tumour they underwent external pituitary irradiation. The one patient (case 2) with evidence of a bulging diaphragma sellae had a further air encephalogram after three months, before attempting to become pregnant, to confirm that no further suprasellar extension had occurred.

Bromocriptine treatment was given to all patients, starting with a dose of 2·5 mg at night and increasing to 5·0-7·5 mg/day at intervals of three to seven days (see table). All patients were advised to take mechanical contraceptive precautions after the start of bromocriptine treatment and wait until at least three regular monthly menstrual cycles had occurred before trying to conceive. After attempts to conceive were started they were advised to stop bromocriptine as soon as the first period had been missed. One patient (case 12) was treated before all the animal evidence excluding teratogenic effects of bromocriptine was available. As she had not conceived after clomiphene treatment alone we decided to give her bromocriptine until regular menstruation and apparent ovulation were present (biphasic temperature chart). She then stopped bromocriptine and contraceptive precautions and was immediately started on a course of clomiphene (150 mg/day for five days) and human chorionic gonadotrophin (HCG; 4500 units on day 12). She immediately conceived. The fetus was not therefore exposed to bromocriptine. This patient again developed galactorrhoea and anovular amenorrhoea after delivery and was restarted on bromocriptine. She successfully conceived a second time while on bromocriptine alone.

All patients had their visual fields plotted during their initial investigations and treatment and then every month throughout pregnancy.

Radiotherapy—Five patients (cases 1-5) had pituitary irradiation as a planned procedure to deliver a lesion dose of 4500 rads in 25 fractions in 35 days. The treatment was carried out with 4 MeV and 15 MeV linear accelerators by a three-field technique individually planned with full isodosimetry so that treatment was localised to the pituitary and the radiation dose to the hypothalamus, brain stem, and temporal lobes kept to a minimum.

Results

Results are summarised on the table. Basal gonadotrophin levels and the responses to Gn-RH were normal or excessive in all patients tested before treatment. Normal gonadal function was restored in all patients after three weeks to six months on bromocriptine 5-7·5 mg/day. Galactorrhoea was abolished in all patients who had suffered it.

All 13 pregnancies occurred within six months, and ten patients conceived within two months. There were no multiple pregnancies, and all 10 babies born at the time of writing have been normal. The pregnancies were uneventful in all but three cases (1, 4, and 12). In case 1 there was evidence during the 38th week of a temporal field loss to red but not to white in the left eye. Labour was therefore induced and the field loss disappeared after delivery. Because of suspected disproportion one patient (case 4) had an elective caesarian section. In case 12 there was a spontaneous leak of liquor at the end of the second trimester and the patient was therefore treated with bed rest for the last trimester and subsequently underwent caesarian section for placenta praevia.

Exposure to bromocriptine after conception—Three patients stopped bromocriptine when their expected period was overdue by 24-48 hours. The other patients continued it for up to 36 days.

Breast-feeding—Patients with apparent pituitary tumours were discouraged from breast-feeding because of the suspected stimulatory effects of feeding on the pituitary. Four of the other patients attempted to breast-feed and three developed painful and grossly engorged breasts. Lactation was successfully suppressed in ten patients with bromocriptine. Two patients were able to breast-feed successfully.

Resumption of gonadal function after delivery—The four patients with pituitary tumours who delivered were restarted on bromocriptine after delivery, and periods returned after two months. Of the remaining six patients who delivered two resumed menstruation spontaneously. The remainder were given bromocriptine for suppression of lactation and their periods started again after five to seven weeks.

Discussion

The advent of a sensitive radioimmunoassay for prolactin has made it possible to identify a large group of patients who present with infertility and who have disorders of prolactin secretion. This group is heterogenous, however, and includes patients with hypothalamic diseases, pituitary tumours, drug-

Clinical data and serum prolactin levels in 12 infertile patients treated with bromocriptine

Case No	Aetiology	Age (years)	Parity	Months of amenorrhoea	Months of galactorrhoea	Serum prolactin (μg/l)		Pituitary irradiation	Dose of bromocriptine (mg/day)	Interval to menstruation (months)	Duration of treatment (months)	Interval to conception (weeks)	Sex of baby	Weeks of breast-feeding	Suppression of lactation with bromocriptine
						Before treatment	On treatment								
1	SPT	36	0	192	11	203	18	+	5	6	20	8	Boy	0	+
2	SPT	26	1	24	0‡		<4	+	5	1	20	4	Boy	0	+
3	SPT	26	0	72	8	88	10	+	7·5	1·5	24	8	Girl	0	+
4	SPT	24	0	48†	48	13	<4	+	5	1 (N)	4	16	Boy	0	+
5	SPT	32	1	60†	96	65	7	+	7·5	1 (N)	4	4	Not delivered	—	
6	Post partum	38	1	48†	18	8		−	5	3 (N)	15	8	Girl	0	+
7	Post partum	28	1	52	9	62	9·0	−	7·5	·75	5	8	Boy	0	+
8	OC	27	0	68	48	102	10	−	7·5	1·5	8	24	Boy	1·5	+
9	OC	23	0	6		8	<4	−	7·5	Pregnant	1·25	5	Boy	4	−
10	Unknown	27	0	24	18	44	12	−	6	·75	11	2	Girl	26	−
11	Unknown	26	0	30	30	>63		−	5	1	4	4	Not delivered	—	
12a*	PCO	24	0	24	18	>63	8	−	6	2	5	4	Boy	26	+
12b	PCO	26	1	3	3	>63	8	−	7·5	1	5	8	Not delivered	—	

*Pregnancy with clomiphene immediately after bromocriptine.
†Dysfunctional bleeding (irregular, often heavy menstruation).
‡Found on examination.
SPT = Suspected pituitary tumour. OC = Amenorrhoea after taking oral contraceptives. PCO = Polycystic ovary syndrome. N = Periods became normal.

induced galactorrhoea and amenorrhoea, and amenorrhoea after oral contraception and some without overt disease. We have found that if prolactin levels are raised and the gonadotrophin reserve is normal after Gn-RH then bromocriptine will restore normal gonadal function. We have also treated patients with normal immunoreactive prolactin levels in whom gonadal functions have returned to normal after suppression of prolactin with bromocriptine.

VISUAL FIELD DEFECTS

Because of the danger of visual field defects, or even blindness, during pregnancy induced by exogenous gonadotrophins in patients with pituitary tumours[8-12] we adopted a cautious and anticipatory policy and accepted any of the following as an indication to proceed to air encephalography: any slight abnormality of the pituitary fossa on plain skull *x*-ray film or tomograms of the fossa; any reduction of anterior pituitary reserve for GH and ACTH during insulin-induced hypoglycaemia[13]; TSH during a TRH test[13 19]; or LH and FSH after Gn-RH.[17-18] Evidence of suprasellar extension was sought and the distance between the diaphragma sellae and the optic nerves gauged. If there was any evidence for the existence of a pituitary tumour the patient underwent external pituitary irradiation in the hope that it would prevent swelling of the gland during pregnancy.

In our small series we did not see any serious visual deterioration during pregnancy, but the central visual fields must be assessed regularly during pregnancy and we obtained field plots every four weeks. One patient had labour induced at 38 weeks because of a minor field defect to red vision only, which then reversed. She had, however, shown variable visual fields before her pregnancy, including similar changes, and the change at 38 weeks may not have been significant. This policy may be criticised for being too conservative and arbitrary, but the development of a field defect during pregnancy is a serious complication, and it should be avoided if possible. Some patients have progressed almost to blindness, although vision usually improves after delivery. It has recently been suggested that, except in patients with ballooned fossae, the clinical situation can be left until field defects occur and then they can be dealt with by pituitary implants of radioactive yttrium.[21] We do not agree with this.

IRRADIATION

We cannot prove that external irradiation offsets the risks of rapid enlargement of a pituitary tumour, but it seems a wise precaution if it can be shown to carry a sufficiently low risk of adverse effects. The treatment was carefully planned with full isodosimetry for each patient, the smallest appropriate fields were used so as to spare vital structures, and the dose was assessed at each point in the irradiated volume. The use of an *x*-ray treatment simulator in planning is essential; so too are exact immobilisation and routine *x*-ray checks on the accuracy of positioning during the treatment. No patient in this series had an adverse reaction during treatment, other than transient headaches in some cases and local epilation in the treatment fields lasting a few months. Radiation effects have rarely been recorded as early as 14 weeks after irradiation,[22] but the long-term risks to be considered are neurological deficit in the hypothalamus, optic tracts, brain stem, or temporal lobes; hypopituitarism; and radiation-induced neoplasm.

No long term ill-effects have occurred in 118 patients irradiated by this technique in this department since 1961. Forty-nine of these patients were treated more than five years earlier, and the latent period for radiation-induced neurological deficit is usually one to five years. At a pituitary dose of 4500 rads in 35 days induced hypopituitarism is unlikely to occur unless a tumour has already destroyed much of the gland. Finally, radiation-induced neoplasm after irradiation of pituitary tumours is extremely rare and has been recorded only many years after high and repeated doses of a different order from those we used.[23] Hence we considered that pituitary irradiation by this technique was a justifiable component in the management of these patients.

Clearly minor abnormalities of the pituitary fossa, usually accepted as being within normal limits, such as a slight asymmetry or dip in the floor on *x*-ray examination, must be considered to be significant in this clinical context.[8 10 11 20 24-26] It is also possible that patients with normal fossae may have microadenomata. As Cushing originally noted, visual field defects may occur as a result of rapid expansion of a tumour which lies in what has been previously considered to be a normal pituitary fossa since such a tumour is more likely to enlarge upwards than one present in a ballooned fossa.[10 12 27] Such rapid expansion may occur in pregnancy.

RESTORATION OF FERTILITY

The restoration of normal fertility in this group of patients has been a major problem in the past, treatment having been largely with exogenous gonadotrophin. From our experience it appears that only patients who are deficient in gonadotrophins but have normal prolactin levels need to be treated with exogenous gonadotrophins. Patients with hyperprolactinaemia rarely ovulate on clomiphene treatment unless prolactin levels are reduced to normal. Patients with raised prolactin levels and a normal gonadotrophin reserve will regularly respond to bromocriptine, and normal gonadal function is usually restored within two months of starting treatment. Some normoprolactinaemic patients also seem to respond successfully to bromocriptine if their basal gonadotrophin levels are normal. Since there is no evidence that bromocriptine itself alters gonadotrophin secretion we must presume that the reduction of the normal immunoreactive prolactin concentrations in these patients is enough to improve their fertility. Alternatively bromocriptine may act on dopaminergic receptors in the gonad.

Bromocriptine treatment in patients with infertility due to various causes has resulted in a rapid return of normal gonadal function and restoration of fertility. There were no multiple pregnancies, and, unlike gonadotrophin therapy, this treatment does not require daily monitoring of blood or urine to avoid overstimulation of the ovaries. There is no clinical or experimental evidence to suggest that bromocriptine is teratogenic[28] but treatment should be withdrawn at the first sign of pregnancy.

We are grateful to the late Dr E R Evans and Dr W M Maclay of Sandoz Products Ltd, who provided the bromocriptine; to our colleagues who referred the patients; to Mr M Phillips and Mrs Enid Taylor for the visual field assessments; and to Miss Janet Hook and the staffs of the metabolic unit and department of chemical pathology for their technical help. These studies are supported by the Joint Research Board of St Bartholomew's Hospital, the Peel Medical Research Trust, and the Medical Research Council.

References

1 Luttberbeck, P M, *et al*, *British Medical Journal*, 1971, **3**, 228.
2 Besser, *et al*, *British Medical Journal*, 1972, **3**, 669.
3 Leutenegger, M, *et al*, *Schweizerische Rundschau für Medizin*, 1972, **23**, 762.
4 Varga, L, Wenner, R, and Del Pozo, E, *American Journal of Obstetrics and Gynaecolcgy*, 1973, **117**, 75.
5 Thorner, M O, *et al*, *British Medical Journal*, 1974, **2**, 419.
6 Del Pozo, E, *et al*, *Journal of Clinical Endocrinology and Metabolism*, 1974, **39**, 18.
7 Tyson, J E, *et al*, *American Journal of Obstetrics and Gynaecology*, 1975, **121**, 375.
8 Kajtar, T, and Tomkin, G H, *British Medical Journal*, 1971, **4**, 88.
9 Swyer, G I M, Little, V, and Harries, B J, *British Medical Journal*, 1971, **4**, 90.
10 Burke, C W, Joplin, G F, and Fraser, R, *Proceedings of the Royal Society of Medicine*, 1972, **65**, 486.
11 Gemzell, C, *American Journal of Obstetrics and Gynecology*, 1975, **121**, 311.
12 Joplin, G F, *et al*, *Clinical Endocrinology*, 1975, **4**, 139.
13 Hall, R, *et al*, *Lancet*, 1972, **1**, 759.

[14] McNeilly, A S, *Proceedings of the Royal Society of Medicine*, 1973, 66, 863
[15] McNeilly, A S, and Hagen, C, *Clinical Endocrinology*, 1974, 3, 427.
[16] Mattingly, D, *Journal of Clinical Pathology*, 1962, 15, 374.
[17] Besser, G M, *et al*, *British Medical Journal*, 1972, 4, 73.
[18] Mortimer, C H, *et al*, *British Medical Journal*, 1973, 4, 73.
[19] Ormston, B J, *et al*, *Lancet*, 1971, 2, 10.
[20] Hardy, J, in *Diagnosis and Treatment of Pituitary Tumours*. ed P O Kohler and G T Ross, p 179. Amsterdam, Excerpta Medica, 1973.
[21] Child, D F, *et al*, *British Medical Journal*, 1975, 4, 87.
[22] Munro, P, and Mair, W G, *Acta Neuropathologica*, 1968, 11, 267.
[23] Greenhouse, A H, *Journal of the American Medical Association*, 1964, 190, 269.
[24] Swanson, H A, and du Boulay, G, *British Journal of Radiology*, 1975, 48, 366.
[25] Besser, G M, *British Journal of Radiology*, in press.
[26] Du Boulay, G, *British Journal of Radiology*, in press.
[27] Cushing, H, *Archives of Internal Medicine*, 1933, 51, 487.
[28] Griffith, R, (Sandoz Products Ltd), 1975, personal communication.

Outside Europe

Bites by puff-adder (Bitis arietans) in Nigeria, and value of antivenom

D A WARRELL, L D ORMEROD, N McD DAVIDSON

British Medical Journal, 1975, 4, 697-700

Summary

Ten patients bitten by the puff-adder (Bitis arietans) were studied in the North of Nigeria. Six showed severe local signs, and four also had evidence of systemic envenoming, including spontaneous bleeding with thrombocytopenia, hypotension, and bradycardia. Two patients died after developing circulatory collapse and renal failure. Antivenom and intravenous fluid restored blood pressure in two hypotensive patients, and antivenom probably prevented the development of local necrosis in four others with massive local swelling. Victims of B arietans who have swelling of more than half the bitten limb or show signs of systemic envenoming should be given at least 80 ml of specific polyvalent antivenom and watched carefully for signs of circulatory collapse. Debridement of necrotic tissue may be necessary.

Introduction

The puff-adder (*Bitis arietans*) (fig 1), which is probably the most common and widespread African snake (fig 2), has been accused of causing more bites and deaths in man and domestic animals than all the other African snakes put together.[1 2] Despite this there have been few clinical studies of patients with proved puff-adder bite.

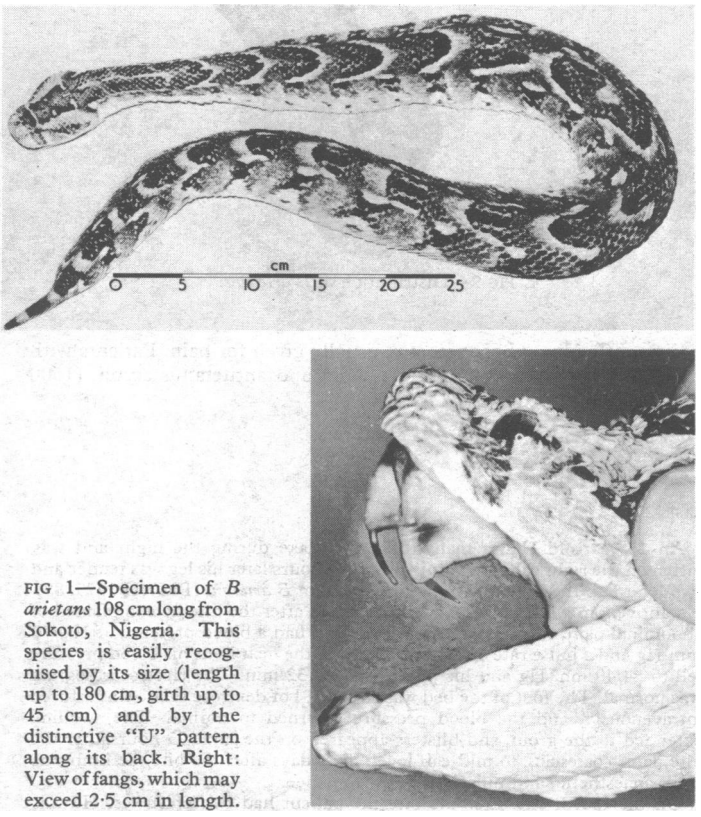

FIG 1—Specimen of *B arietans* 108 cm long from Sokoto, Nigeria. This species is easily recognised by its size (length up to 180 cm, girth up to 45 cm) and by the distinctive "U" pattern along its back. Right: View of fangs, which may exceed 2·5 cm in length.

Patients and methods

Ten patients with proved *B arietans* bite (table) were admitted to Ahmadu Bello University Hospital, Zaria, between 1971 and 1974. Eight brought the snake, which ranged in length from 30 to 132 cm (mean 86·8 cm), for identification. Seven of these have been deposited in the British Museum (Natural History) (accession numbers BMNH 1975. 21-26 and 88). The other two cases were diagnosed by detecting *B arietans* venom in fluid aspirated from the site of the bite and in the urine.[3] Methods for clinical assessment and laboratory investigation have been described.[4 5]

Department of Medicine, Ahmadu Bello University, Zaria, Nigeria
D A WARRELL, DM, MRCP, senior lecturer in medicine (now consultant physician, Radcliffe Infirmary, Oxford)
L D ORMEROD, MB, MRCP, medical registrar (now senior house officer, Western Ophthalmic Hospital, London)
N McD DAVIDSON, BM, MRCP, senior lecturer in medicine (now lecturer in medicine, Western General Hospital, Edinburgh)

Treatment

Seven patients were given specific polyvalent antivenom intravenously over 10-30 minutes (table) (Behringwerke, *Bitis, Echis, Naja*; FitzSimons, *Bitis, Hemachatus, Naja;* South African Institute for Medical Research (SAIMR), *Bitis, Dendroaspis, Hemachatus*). Two others (cases 7 and 10) were thought not to need it, and it was not available in case 2. Bitten limbs were rested in the most comfortable