- 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.

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

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.

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}

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

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)

Clinical details of 10 patients bitten by *B arietans*

Case No	Age (years)	Site of bite	Time from bite to admission (h)	Antivenom‡	Extent (grade) 1-6	Local swelling		Time blistering appeared after bite	Time necrosis detected after bite
						Circumference increase (cm)	% control limb		
1*	55	Calf	2	B40	5	20.7	19		
2*	18	Calf	3		6	27.0	25	23 h	17½ h
3	27	Calf	3½	B80	5	28.8	24	2 d	48 h
4	7	Hand	5½	S40	6	8.9	28	22 h	
5	20	Calf	2	B40, F20, S20	5	26.2	22	2 d	
6	24	Ankle	½	B40	5	40.3	26		
7	25	Thumb	5 weeks		3	?	?	2 d	1 week
8	30	Toe	3	B40	2	?	?		
9	10	Ankle	2	B40	1	?	?		
10†	9	Heel	34½		1	1.9	6		

*Fatal cases.
†Girl patient.
‡Antivenom: B = Behringwerke. F = FitzSimons. S = SAIMR.

FIG 2—Distribution of *B arietans*.

position. Codeine phosphate was usually given for pain. Patients with necrosis were given procaine penicillin and antitetanus serum (1500 units).

Case reports

CASE 2

An 18-year-old Hausa man trod on a snake during the night and was bitten on the right calf. On admission three hours later his leg was tender and swollen to up the knee. He brought the 82-cm *B arietans* (BMNH 1975. 88). No antivenom was available. Eighteen hours after the bite he complained of abdominal pain, was cold and sweating, and had a blood pressure of 100/70 mm Hg and a pulse rate of 110/min. During the next hour his blood pressure fell to 84/40 mm Hg and his pulse rose to 132/min. The electrocardiogram was normal. The foot of the bed was raised, 1 l of dextrose saline was infused intravenously, and the blood pressure returned to normal. The swelling extended to the groin, and blisters appeared on the ankle 25 hours after the bite, later coalescing to mid-calf level. Two days after the bite the limb was cold, anaesthetic, and pulseless below the knee.

On the fourth day after the bite the patient had two epistaxes. He was severely anaemic with a haemoglobin of 3.6 g/dl, and there was a leucocytosis of $11.4 \times 10^9/l$. Poikilocytes and schistocytes were seen in the blood film, suggesting microangiopathic haemolysis. The blood was coagulable and clot quality was normal. One unit of fresh blood was transfused without reaction. Although the limb had become frankly gangrenous, amputation was vigorously opposed by his relatives. On the seventh day pitting oedema extended up to the chest wall. Haemoglobin had risen slightly and his platelet count was $278 \times 10^9/l$ but he had further arterial epistaxes and became jaundiced. Two units of blood were transfused. By the twelfth day his blood urea was 35.5 mmol/l (214 mg/100 ml). On the twenty-third day his relatives agreed to amputation. Postoperatively he developed paralytic ileus; plasma potassium and urea concentrations continued to rise and he died in ventricular fibrillation 24 days after being bitten.

CASE 4

A 7-year-old Mangu boy was bitten on the right hand by a 118-cm *B arietans* (BMNH 1975. 22) while cutting grass. On admission five-and-a-

half hours later he was drowsy but rousable and had no neurological defects. Blood pressure was 90/20 mm Hg and the pulse 124/min and regular. One fang mark was visible in the first interdigital cleft. There was tender oedema of the entire right arm including the pectoral and scapular regions (fig 3 a). Enlarged tender lymph nodes were palpable in the right axilla. Haemoglobin was 10 g/dl, platelets were $186 \times 10^9/l$, and leucocytes were $16.2 \times 10^9/l$ (83% neutrophils). He was given 40 ml of SAIMR antivenom. Thirteen hours after the bite an ecchymosis appeared in the right axilla, and 22 hours after the bite blood-filled blisters appeared on the palm and dorsum of the hand (fig 3 b). Thirty-five hours after the bite tender swelling extended down the right flank; the right inguinal nodes were painfully enlarged. New blisters erupted up to three days after the bite, his temperature rose to 50.4°C, and he was given penicillin. His haemoglobin fell to 7.4 g/dl and he was transfused.

FIG 3—Case 4. Seven-year-old boy bitten in first interdigital cleft by *B arietans*. (a) Appearances on admission, five-and-a-half hours after bite. There is extensive swelling of chest wall. (b) Appearances 22 hours after bite, with extensive blistering of hand and wrist. (c) Appearances four weeks after bite. Patient was completely recovered, with no tissue necrosis.

By the sixth day after the bite his temperature had fallen to normal and the swelling had decreased. The blisters gradually dried up without necrosis. He was discharged 16 days after being bitten, and two weeks later a small scab on the right palm was the only evidence of the bite (fig 3 c).

Results

Clinical—Local pain and swelling were noticed by all patients within 20 minutes of being bitten. Three vomited, but one had taken a herbal emetic. Fang punctures 1.5–5 cm (mean 3.6 cm) apart were found in four cases. Local swelling (table) was maximal one or two days after the bite and took five days to three weeks to resolve. Local blistering was seen in five cases and necrosis in three. Popliteal artery thrombosis was a complication in case 2. Spontaneous systemic bleeding occurred in three patients—one (case 1) bled from healthy gums four hours after the bite (and into the aortic adventitia, found at necropsy), and two had epistaxes, one (case 2) on the fourth, ninth, and tenth days, and the other (case 5) on the fourth day. In cases 3 and 4 the patients developed ecchymoses in the bitten limb. No blood was found in vomitus, stool, or urine. Five patients (cases 1–5) had fever on admission, reaching 38.7°–40.5°C (mean 39.3°C) up to eight days after the bite. Although four patients were drowsy on admission, all were fully rousable, and no other neurological abnormalities were found. Hypotension was observed in case 2; in case 1, in which the blood pressure fell before death (ECG was normal 13 hours earlier); and in case 3, in which the patient had a blood pressure of 90/50 mm Hg and a bradycardia of 52/min on admission. In cases 2 and 3 the patients became jaundiced on the ninth and fourth days respectively.

Investigations—A neutrophil leucocytosis was found in five of the six patients examined. Maximum total white cell counts of $8.5\text{--}13.6 \times 10^9/\text{l}$ were seen within six days of the bite (normal $5492 \times 10^9 \pm 2.061 \times 10^9/\text{l}$). Anaemia developed in cases 2 and 4 and in case 3, in which the haemoglobin fell from 15.0 to 8.9 g/dl on the second day after the bite. Possible causes included microangiopathic haemolysis and epistaxis (case 2) and bleeding into the bitten limb (cases 2, 3, and 4). Thrombocytopenia was found in three patients (cases 1, 3, and 5; 100×10^9 , 27×10^9 , and $68 \times 10^9/\text{l}$ respectively), who were examined two to four hours after the bite (normal $186.052 \times 10^9 \pm 41.547 \times 10^9/\text{l}$). The first patient died before repeat examination, but in cases 3 and 5 the values had returned to normal by the third and second days after the bite. The remaining patients had values ranging from 160×10^9 to $278 \times 10^9/\text{l}$ throughout their stay. Blood was coagulable in all nine cases tested; the clot quality was normal (grade 1). In case 1 dilute whole blood clot lysis time was reduced to 65 minutes and the whole blood clot was completely lysed in six hours. Clot lysis was normal in the other two patients tested (cases 6 and 10).

Clotting factors—In cases 3 and 5 fibrinogen and factors II, V, VII, VIII, and X were measured on admission and on three subsequent occasions before discharge two weeks later. Values were within or above the normal range and showed no particular trend after admission. Grade 1 clot quality implied normal fibrinogen levels in seven other cases. Fibrin degradation products were measured in cases 3, 4, 6, and 10. Values ranged from 1.25 to 10 mg/l. Plasma electrolytes and urea remained normal in all except case 2.

Antivenom treatment—Two of the seven patients given antivenom (table) (cases 9 and 8) had signs of mild local envenoming only, and in retrospect did not require treatment. As it happened these were the only patients to suffer immediate-type serum reactions. Four patients who showed evidence of severe envenoming but recovered without tissue necrosis (cases 3–6) were given 40–80 ml of antivenom. Swelling affected the whole limb (circumference increases 22–28%), three developed blisters, two local bruising, and one systemic bleeding; two had thrombocytopenia. One patient (case 3) was admitted with hypotension and bradycardia; after receiving 80 ml of antivenom his blood pressure rose by 60 mm Hg and his pulse rate increased from 52 to 80 beats/min.

Deaths—Two patients died. One (case 2) who could not be given antivenom is described above. The other patient (case 1; table) was given 40 ml of antivenom two-and-a-half hours after the bite. Eight hours later the blood pressure was 110/75 mm Hg, pulse rate 100/min, and ECG normal, but 16 hours after the bite the blood pressure fell to 85/50 mm Hg and he died one hour later. Necropsy failed to show a cause of death.

Discussion

The local effects of venom seen in our patients—swelling, blistering, bruising, arterial thrombosis, and necrosis—are well

known.^{6–11} Many of the cases in Chapman's large series¹⁰ were diagnosed by their clinical signs alone, so that other species may have been responsible.⁵ Chapman attributed the severe hypotension observed in some victims of *B. arietans*^{9 10 12} to massive haemorrhage into the bitten limb, chest wall, gut, and pelvis.^{10 13} This was not the explanation in our case 1, in which the patient died of circulatory collapse without appreciable blood loss. A direct action of venom on the myocardium or autonomic nervous system may have been responsible. In animals *B. arietans* venom causes hypotension and bradycardia variously explained^{14 15} by reflex vasodilatation, myocardial depression, and increased capillary permeability. In case 3 hypotension and bradycardia responded to antivenom alone, and in case 1 hypotension and tachycardia were relieved by intravenous fluid.

B. arietans venom is selectively bound by the kidney and causes haematuria in animals,¹⁶ so that a direct action of venom may have contributed to the renal failure in case 2. Fibrinolytic enzymes in the venom cause the blood to become incoagulable in vitro,^{17–19} envenomed animals show features of disseminated intravascular coagulation (DIC),^{11 20} and in one human victim there was a mild coagulation disturbance.¹¹ Two Ugandan patients, thought to have been bitten by *B. arietans* showed gross haemostatic abnormalities attributed to DIC, but several discordant features of these cases throw some doubt on the diagnosis and pathological interpretation.²¹ The present series of patients, including six with severe local and systemic envenoming (two of whom died), showed no evidence of DIC; though three had thrombocytopenia and one showed increased fibrinolytic activity, the levels of clotting factors and fibrin degradation products were normal. Spontaneous haemorrhage is more likely to be due to a damaging effect of the venom on vascular endothelium aggravated by thrombocytopenia.

The danger of *B. arietans* bite is emphasised by the two deaths in this series and by other deaths reported.^{10 13 22–25} In view of the risk of sudden and delayed collapse (as in case 1) patients should be admitted to hospital and their blood pressure and pulse rate measured frequently for at least 48 hours after the bite. From our experience, and in the absence of a controlled study, we suggest that at least 80 ml of specific antivenom should be given to patients bitten by *B. arietans* when there are signs of systemic envenoming (spontaneous bleeding, thrombocytopenia, hypotension, and bradycardia) or when local swelling affects more than half of the limb. Antivenom is effective in relieving hypotension and bradycardia provided that the circulating volume is restored with intravenous fluid, preferably fresh whole blood or plasma expanders. Antivenoms are not thought to prevent local tissue damage,²⁶ though four of our patients (cases 3–6) who had severe local envenoming, including swelling of the whole limb and blistering, did not develop necrosis. This we attribute to the early use of specific antivenom. If necrosis does develop immediate extensive surgical debridement followed by split skin grafting should be performed and the patients protected from secondary infection by antibiotics and antitetanus serum. Neglected cases may result in extensive tissue destruction with chronic ulceration (fig 4). The use of corticosteroids and pressure-relieving incisions (fasciotomy) for tensely oedematous limbs seems rational but adds to the risk of local infection and blood loss and is unsupported by sound evidence.¹⁰

FIG 4—Neglected case (not included in series) with extensive ulceration. Patient arrived at hospital eight weeks after being bitten.

In the West African savanna bites by at least two other snakes—the carpet viper (*Echis carinatus*) and the spitting cobra (*Naja nigricollis*)—may cause spontaneous haemorrhage, extensive local swelling, blistering, and necrosis. When the snake is not identified diagnosis may be helped by immunological studies³ or by a simple clotting test.⁴ Incoagulable blood indicates systemic envenoming by *E. carinatus* and failure of clot retraction may suggest *N. nigricollis*.⁵

This work was supported by the Wellcome Trust. We are grateful to Miss Helen Pope and Miss Barbara Watkins for technical help, to Professor G M Edington for the necropsy in case, 1 to Dr C R M Prentice for measurement of clotting factors in cases 3 and 5, and to Dr H A Reid for helpful discussion and encouragement.

References

- ¹ FitzSimons, V F M, *Snakes of Southern Africa*, p 337. London, MacDonald, 1962.
- ² Broadley, D G, *Venomous Animals and their Venoms*, ed W Bucherl, E Buckley, and V Deulofeu, vol 1, p 433. New York, Academic Press, 1968.
- ³ Greenwood, B M, *et al*, *British Medical Journal*, 1974, 4, 743.
- ⁴ Warrell, D A, *et al*, *British Medical Journal*, 1974, 4, 437.
- ⁵ Warrell, D A, *et al*, *Quarterly Journal of Medicine*, 1976, 45, 1.
- ⁶ Pluyette, E, *Bulletins et Mémoires de la Société des Chirugiens de Paris*, 1886, 12, 779.
- ⁷ Calmette, A, *Venoms, Venomous Animals and Anti-venomous Serum-therapeutics*, p 350. London, Bale and Danielsson, 1908.
- ⁸ Strover, H M, *Central African Journal of Medicine*, 1961, 7, 84.
- ⁹ Visser, J, *Poisonous Snakes of Southern Africa and the Treatment of Snake Bite*, 2nd edn, p 39. Cape Town, Timmins, 1967.
- ¹⁰ Chapman, D S, *Venomous Animals and their Venoms*, ed W Bucherl, E Buckley, and V Deulofeu, vol 1, p 463. New York, Academic Press, 1968.
- ¹¹ Phillips, L L, *et al*, *Toxicon*, 1973, 11, 423.
- ¹² Whitty, J A, *British Medical Journal*, 1889, 1, 1226.
- ¹³ Leeson, F, *Identification of Snakes of the Gold Coast*, plate xxi. London, Crown Agents, 1950.

- ¹⁴ Vick, J A, Ciuchta, H P, and Manthei, J H, *Animal Toxins*, ed F E Russell, and P R Saunders, p 269. Oxford, Pergamon, 1967.
- ¹⁵ Osman, O H, and Gumaa, K A, *Toxicon*, 1974, 12, 569.
- ¹⁶ Gumaa, K A, Osman, O H, and Kertesz, G, *Toxicon*, 1974, 12, 569.
- ¹⁷ Baujean, R, *Bulletin de la Société de Pathologie Exotique*, 1913, 6, 50.
- ¹⁸ Link, T, *Zeitschrift für Immunitätsforschung, Allergie und Klinische Immunologie*, 1935, 85, 405.
- ¹⁹ Eagle, H, *Journal of Experimental Medicine*, 1937, 65, 613.
- ²⁰ Brink, S, and Steyler, J G, *South African Medical Journal*, 1974, 48, 1205.
- ²¹ Sezi, C L, Alpidovsky, V K, and Reeve, M I, *East African Medical Journal*, 1972, 49, 589.
- ²² FitzSimons, F W, *The Snakes of South Africa; their Venom and the Treatment of Snake Bite*, p 230. Cape Town, Miller, 1912.
- ²³ Bloss, J, *Sudan Notes and Records*, 1951, 32, 173.
- ²⁴ Owen, J S, *Sudan Notes and Records*, 1952, 33, 311.
- ²⁵ Christy, N P, *American Journal of Medicine*, 1967, 42, 107.
- ²⁶ Homma, M, and Tu, A T, *American Journal of Tropical Medicine and Hygiene*, 1970, 19, 880.

How soon may a patient take strenuous exercise, such as playing tennis, after an uncomplicated attack of infectious hepatitis?

Commonsense advice for patients with acute infectious hepatitis is that they should be treated with bedrest for as long as the acute symptoms persist. Depending on the severity of the attack, this means restriction to the confines of their homes or hospital ward until their liver function tests are approaching normality (particularly reduction in serum bilirubin to <2 mg/100 ml). Subsequently, after adequate convalescence—usually recommended to be equal in time to duration of acute illness—exercise may be undertaken with safety. In the controlled trial carried out by Chalmers and colleagues there was no evidence that such activity either precipitates a recurrence of the acute attack¹ or renders the patient more susceptible to the development of chronic liver disease.²

- ¹ Chalmers, T C, *et al*, *Journal of Clinical Investigation*, 1955, 34, 1163.
- ² Nefzger, M D, and Chalmers, T C, *American Journal of Medicine*, 1963, 35, 299.

Christmas Quiz, 1975

This year we are offering copies of the *Personal View* anthology for the first five correct answers opened on Wednesday, 7 January.

Answers will be given in the issue of 17 January.

- What have the following in common?
 - (a) Toilet seat, gunbelt, guitar, ski boot, grocery bag.
 - (b) Writer, musician, telegraphist, seamstress, bowler (in cricket).
 - (c) Albert Camus, *The Story of San Michele*, Daniel Defoe, *The Decameron*.
 - (d) Sucked candy syndrome, waters of Bath, the church of Santa Maria di Nazareth in Venice, homo planus.
 and which is the odd man out?
 - (e) Alexander's syndrome, Fitzgerald trait, Fletcher deficiency, Hagemann factor, Heckathorn's disease, Passovoy factor.
- What dangers are involved in?
 - (a) Popple peeler's disease. (b) Negev desert lung. (c) Huffer's neuropathy. (d) Saturday night retinopathy. (e) Bullman's hand. (f) Degreaser's flush. (g) Tweedle's disease. (h) Green tobacco sickness. (i) Sucking socks syndrome. (j) Vick vapour rub intoxication.
- Name the following whose anniversaries occurred in 1975:
 - (a) The interpreter of dreams.
 - (b) An organist who won the Nobel Peace Prize for his work in Africa.
 - (c) A physicist known to every medical student for his bridge.
 - (d) A physician involved in a plot to restore the Stuarts and released from the Tower on the intervention of Richard Mead.
 - (e) The medical officer of the first Everest expedition.
 - (f) A Dublin physician who described the features of heart block.
- What are?
 - (a) Apudoma. (b) Anisakiasis. (c) Linguatuliasis. (d) Marantic vegetations. (e) Manus apostolicus. (f) Scombroid. (g) Epluchage.
- What doctor?
 - (a) Made the first journey by road in a steam carriage.
 - (b) Discovered diamonds.
 - (c) Weighed 32 stone.
 - (d) Introduced algebra.
 - (e) Founded the Boston Medical Library a hundred years ago.
 - (f) Made the first recording of an electrocardiogram.
- What are?
 - (a) Atlanta syndrome. (b) Diogenes syndrome. (c) Molaret's meningitis. (d) Locked-in syndrome. (e) Dornford Yates syndrome. (f) Slapped cheek disease. (g) Overlander syndrome.
- The following abbreviations are taken from recently published papers. What do they stand for?
 - (a) BART or PART. (b) COLD. (c) CLUE test. (d) DISH. (e) PEEP. (f) TEN. (g) POLARS.
- For what are the following doctors better known?
 - (a) William Stukeley (1687-1765)
 - (b) Sir William Petty (1623-87)
 - (c) Thomas Gann (1867-1938)
 - (d) Gideon Mantell (1790-1852)
 - (e) John Vaughan Thompson (1779-1847)
 - (f) Nathaniel Ward (1791-1868)