



NEUROTOXICITY AND HAEMOSTATIC DISTURBANCES IN PATIENTS ENVENOMED BY THE PAPUAN BLACK SNAKE (*PSEUDECHIS PAPUANUS*)

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D. LALLOO, A. TREVETT, J. BLACK, J. MAPAO, S. NARAQI, D. OWENS, R. HUTTON, R. D. G. THEAKSTON and D. A. WARRELL. Neurotoxicity and haemostatic disturbances in patients envenomed by the Papuan black snake (*Pseudechis papuanus*). *Toxicon* 32, 927-936, 1994.—Among 335 patients presenting with snakebites in Central Province, Papua New Guinea, nine were proved by enzyme immunoassay to have been bitten by Papuan black snakes (*Pseudechis papuanus*). Seven showed clinical evidence of envenoming. Early symptoms included vomiting and tender local lymph nodes. Five patients had neurotoxic signs and one required mechanical ventilation. Spontaneous systemic bleeding occurred in two patients. Coagulation studies in four patients showed thrombocytopenia, prolongation of prothrombin time, mild defibrination and depletion of other clotting factors with elevated fibrin(ogen) degradation products and other evidence of fibrinolysis. One patient developed mild renal dysfunction. There was no evidence of intravascular haemolysis or rhabdomyolysis. These clinical observations, which do not distinguish victims of *P. papuanus* from those of taipans (*Oxyuranus scutellatus canni*), suggest that the venom contains neurotoxic, haemorrhagic and mild procoagulant activities. Only two other cases of proven envenoming by this species have been reported. There appears to have been a decline in the abundance of this species, and hence its medical importance, over the last 25 years.

INTRODUCTION

THE PAPUAN black snake (*Pseudechis papuanus*) (Fig. 1) is confined to the southern coast of Papua New Guinea and perhaps to the adjacent area of Irian Jaya. During the 1960s, Campbell ascribed to *P. papuanus* the majority of venomous snakebites in Central Province (CAMPBELL, 1967). He described the clinical features in 13 patients who presented

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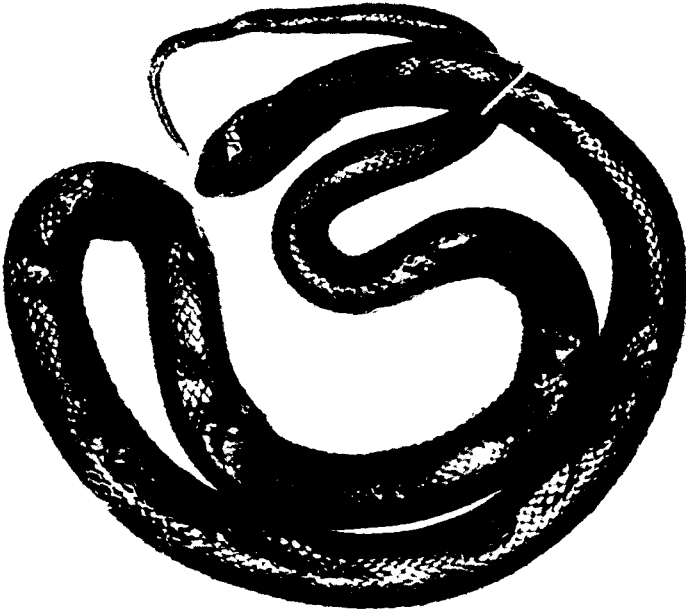


Fig. 1a



Fig. 1b

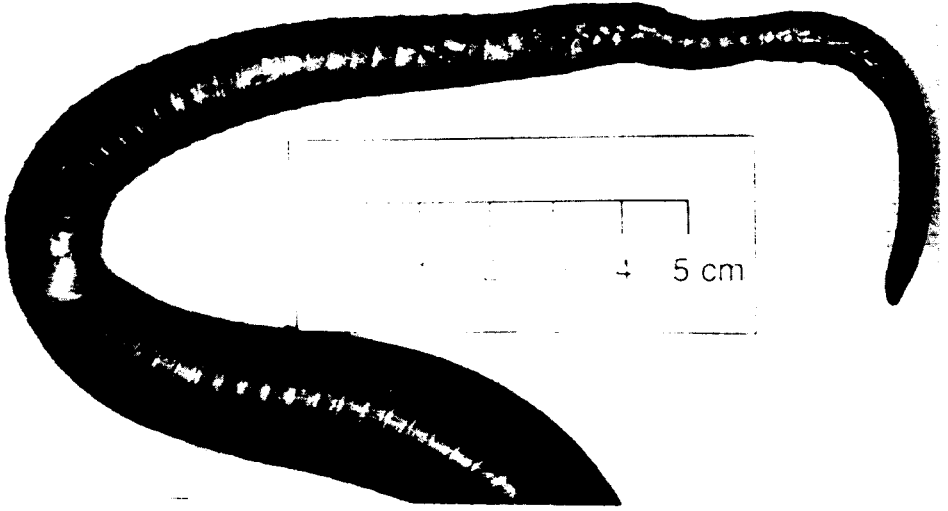


Fig. 1c

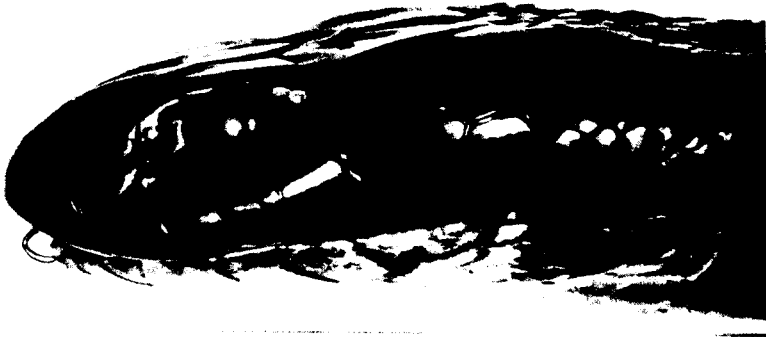


Fig. 1d

FIG. 1. PAPUAN BLACK SNAKE (*Pseudechis papuanus*). Male specimens, total length 1150 mm, collected at Veifa'a, Central Province, Papua New Guinea, in 1991. Scale in cm. (a) Dorsal view; (b) ventral view; (c) detail of ventral surface of tail showing characteristic divided anal scale with entire proximal and divided distal sub-caudal scales; and (d) lateral view of head.

to Port Moresby General Hospital (PMGH) in 1964/1965 with envenoming following presumed bites by this species; vomiting, tender lymphadenopathy, neurotoxicity, incoagulable blood and haemolysis. Identification of the biting species was based mainly on the

patients' description of the snake; the snake was positively identified in only one case and in a second patient seen during the next 7 years (CAMPBELL, 1967). However, in our experience most patients are bitten in long 'kunai' grass and are rarely able to catch more than a glimpse of the fast moving snake which has bitten them. In such circumstances, the victim may not see the characteristic dorsal orange band of the Papuan taipan (*Oxyuranus scutellatus canni*), which is now responsible for most venomous bites in this area (LALLOO *et al.*, 1993). In the present study, we used enzyme immunoassay (EIA) to identify nine patients bitten by *P. papuanus* and describe the clinical and laboratory features associated with envenoming by this species.

MATERIALS AND METHODS

Clinical methods

All patients presenting to PMGH between January 1990 and June 1992 with a history of snakebite were entered into a prospective clinical study. History and examination were recorded on a standard proforma. Blood was taken for routine haematology and biochemistry. Two millilitres of blood was placed in a new, clean, dry, glass test tube for determination of the 20 min whole blood clotting test (20WBCT) (WARRELL *et al.*, 1977). Nine millilitres of blood was added to 1 ml of 130 mM trisodium citrate, immediately centrifuged, separated and frozen in 1.5 ml aliquots at -70°C for measurement of clotting factors. Two millilitres of blood was collected into a FDP (fibrin(ogen) degradation products) tube containing thrombin and soy bean trypsin inhibitor (Wellcome Diagnostics, U.K.). A serum sample, bite wound swab, bite wound aspirate and urine sample were taken and frozen for later determination of venom antigen concentrations. Urine was collected for urinalysis and microscopy.

Patients with signs of envenoming were treated with one ampoule of polyvalent antivenom (Australia-New Guinea, Commonwealth Serum Laboratories, Melbourne, Australia), diluted to a total volume of 100 ml and infused i.v. over 20 min. Patients were nursed on their side in a high dependency ward or the Intensive Care Unit. Ventilation was performed using a Bird Mark 7 pressure cycled ventilator if necessary.

Patients were reviewed every 6 hr after admission for the first 24 hr, and every 12 hr thereafter. Examination was repeated to record the development and progression of neuromuscular involvement in different muscle groups and to observe the response to antivenom. The 20WBCT was repeated every 6 hr.

Laboratory methods

Haemoglobin concentration and white cell counts were measured using a Coulter counter model M450 (Coulter Electronics Ltd, Australia). Platelet counts were performed using a modified Neubauer counting chamber with ammonium oxalate as diluent. Biochemical measurements were made with a Technicon RA 1000 autoanalyser.

Serum, urine and wound aspirates were tested for the presence of venom by EIA using the method of THEAKSTON *et al.* (1977) with the modification described by HO *et al.* (1986). Each sample was tested against *P. papuanus*, *O. s. canni*, *Acanthophis* sp. (death adder), *Pseudonaja textilis* (eastern brown snake) and *Micropechis ikaheka* (small-eyed snake) antisera. Background absorbance was established by assaying 102 samples from individuals who had never been exposed to snakebite but lived under the same conditions as the patients. The mean O.D. and S.E.M. were calculated for these controls, and this mean value +2 S.E.M. was subtracted from the venom levels measured in patients.

Screening tests of haemostasis were performed using standard methods (DENSON, 1972). Fibrinogen was measured by the Clauss method (DENSON, 1969). Other coagulation factor assays were carried out by one-stage assays using the coagulation channel of the ACL 300R coagulometer (Instrumentation Laboratories). ATIII, plasminogen and α_2 antiplasmin were assayed using chromogene substrate kits (Organon Teknika). Enzyme immunoassays (EIA) were used to assay Factor XIIIa and S subunits (MURDOCK *et al.*, 1992), thrombin-antithrombin complexes (Behring), von Willebrand factor and Protein C (using antibodies obtained from Dakopatts, U.K.). Fibrin(ogen) degradation products (FDP) were assayed semi-quantitatively using antibody-coated latex beads (Thrombo Wellcotest, Murex Diagnostics) and serial doubling dilutions of the patients' serum.

RESULTS

EIA revealed that nine of 335 (2.7%) patients presenting with snakebite during the 27 month period had been bitten by *P. papuanus*. Seven (four male, age range 12–60) had clinical features of envenoming. *Pseudechis papuanus* was responsible for 4.2% of all envenomed patients in whom the biting species was diagnosed, taipan 83.2%, death adders 10.8%, common brown snakes 1.8%, and small-eyed snake 0%.

Clinical features

All nine patients with proven bites by *P. papuanus* were bitten on a lower limb during daylight hours; only five were able to describe being bitten by a long black snake. Bites occurred while walking on bush paths or working in gardens. Six patients presented directly to PMGH, the other three were referred from neighbouring health centres.

Table 1 shows the symptoms and signs described by the seven patients with clinical features of envenoming. The first symptoms occurred between 2 and 21 hr after the bite. There was minimal local swelling at the site of the bite and fang marks were often only just visible. Tender enlargement of lymph nodes draining the bitten site was found in six patients, in two this was the only sign present.

Five of the seven clinically envenomed patients showed neurological signs; in four, these were present on admission, but the fifth patient did not develop neurotoxic signs until 11 hr after the bite, several hours after reaching hospital. One patient presented with ptosis, complete ophthalmoplegia, pooling of secretions and minimal respiratory excursion, and required immediate intubation and ventilation.

Non-clotting blood indicated by the 20WBCT was reported by health centre or casualty staff in patients 1 and 2; but their blood was clotting normally when we checked it several

TABLE 1. SYMPTOMS AND SIGNS FOLLOWING BITE BY PAPUAN BLACK SNAKE

	1	2	3	4	Case					Total (n = 9)	CAMPBELL'S* cases (n = 2)
					5	6	7	8	9		
Symptoms, general											
No symptoms								+	+	2	
Lymph node pain	+		+			+	+			4	2
Headache	+						+			2	1
Abdominal pain	+	+			+	+	+			5	2
Vomiting		+		+						2	
Collapse										0	
Drowsiness					+					1	1
Bleeding from nose and mouth	+				+					2	
Symptoms, neurological											
Ptosis	+	+	+	+	+					5	1
Diplopia		+								1	
Dysphagia		+		+	+					3	
Dysarthria	+	+			+					3	
Difficulty in opening mouth				+						1	
Difficulty in breathing					+					1	
Signs											
No signs								+	+	2	
Swelling of bite site										0 (slight swelling)	1
Tender lymph nodes	+		+	+	+	+	+			6	2
Abdominal tenderness	+				+	+				3	
Bloodstained saliva	+									1	
Bleeding from nose				+						1	
Ptosis	+	+	+	+	+					5	1
Ophthalmoplegia	+	+	+	+	+					5	
Jaw restriction				+						1	
Slurred speech	+	+		+	+					4	
Diminished reflexes					+					1	
Diminished hand grip				+	+					2	
Required: intubation					+					1	
ventilation					+					1	

*CAMPBELL (1967); C.H. CAMPBELL (personal communication, 1992).

hours later. Patient 1 reported bleeding from the mouth before admission, but this had ceased by the time of arrival. Patient 5 developed bleeding from the nose 48 hr after the bite which stopped spontaneously within a few hours; the 20WBCT was normal throughout his admission.

Five of the seven patients (numbers 1–4 and 6) with clinical evidence of envenoming were treated with antivenom; taipan antivenom was given to Patient 5 in error. Specific polyvalent antivenom was given at 4.5, 5, 22.5 and approximately 18 hr after the bite. Patient 4 was given antivenom relatively early (5 hr after the bite). The degree of ptosis, ophthalmoplegia and peripheral weakness improved markedly during the next 6 hr, in this patient and in Patient 1 signs of neurotoxicity, including severe ptosis and a complete ophthalmoplegia, had almost resolved within 24 hr of antivenom. In Patient 3, neurotoxicity persisted for 3 days. Recovery seemed to be more rapid than in patients bitten by taipans (LALLOO *et al.*, 1993). Patient 5, who was the most severely affected, received taipan antivenom inappropriately; there was no improvement until 48 hr after antivenom when he regained a flicker of lateral eye movements; he required intubation for 72 hr. All nine patients survived.

Complications of envenoming were rare. Patient 5 developed renal impairment; serum creatinine was 440 μ mol/litre 48 hr after the bite and then returned to normal. Proteinuria and 'haemoglobinuria' (indistinguishable from myoglobinuria) were noted on dipstick testing and granular casts were visible upon microscopy.

Laboratory results

Pseudechis papuanus venom antigen was detected in samples from seven patients with clinical evidence of envenoming and in two patients without apparent envenoming (Table 2). The median serum venom antigen level in envenomed patients was 39.0 ng/ml; the mean background level in controls for this assay was 1 ng/ml. Venom antigen of other species was not detected in any of these samples.

Haemoglobin and white cell counts were normal in all patients during admission. Platelet counts in five patients were normal in three; in Patient 5 the platelet count fell during admission from 113×10^9 /litre to 93×10^9 /litre and, in Patient 1, the platelet count on the day after admission was 91×10^9 /litre (normal range 98 – 335×10^9 /litre).

Serum creatine kinase concentrations were measured in Patients 2, 3, 5 and 6; they were raised in Patients 2 and 3 (372 and 728 IU/litre, respectively, normal <243 IU/litre). The only other biochemical abnormality was in the patient with renal impairment.

TABLE 2. PAPUAN BLACK SNAKE VENOM DETECTION IN NINE PATIENTS

Patient number	Admission venom antigen level (ng/ml)			
	Serum	Urine	Aspirate	Swab
1	26.0	0.0	—	—
2	13.0	10.0	—	—
3	39.0	0.0	—	—
4	47.0	0.0	11.0	—
5	270.0	5.5	—	—
6	15.0	—	0.0	0.0
7	10.0	—	—	—
8*	11.0	—	—	—
9*	6.6	—	—	—

*Patient with no clinical evidence of envenoming.

TABLE 3. COAGULATION STUDIES IN FOUR PATIENTS BITTEN BY PAPUAN BLACK SNAKES

Test	Time after antivenom (hr):	Patient 1	Patient 2	Patient 5	Patient 6	Normal range
		18	8	—	—	
20WBCT		clotted*	clotted*	clotted*	clotted*	
PT (sec)		21.8	17.5	16.8	15.6	12-16
APTT (sec)		64.2	51.7	50.2	45.4	32-47
Fibrinogen (g/litre)		0.98	1.40	1.66	2.31	1.3-4.8
Platelets ($\times 10^9$ /litre)		91		113	277	98-355
Factor II (U/dl)		41	36	62	—	50-200†
Factor V (U/dl)		27	38	44	—	50-200†
Factor VII (U/dl)		50	60	76	—	50-200†
Factor VIII (U/dl)		18	23	26	—	50-200†
Factor IX (U/dl)		32	50	40	—	50-200†
Factor X (U/dl)		60	62	64	—	50-200
Factor XI (U/dl)		45	42	37	—	47-80
Factor XII (U/dl)		26	38	37	—	40-102
Factor XIIIa (U/dl)		4	12	35	—	50-200†
Factor XIIIs (U/dl)		36	35	78	—	50-200†
von Willebrand factor (U/dl)		326	273	92	—	50-200†
Antithrombin III (U/dl)		57	60	80	—	70-140
Protein C (U/dl)		26	73	56	—	70-160
Plasminogen (U/dl)		48	62	73	—	70-180
A ₂ -antiplasmin (U/dl)		52	73	63	—	70-150†
FDP (μ g/ml)		160	80	80	—	< 10
Thrombin-antithrombin (μ g/litre)		242	344	57	—	1.0-11.0†

*Previously reported as non-clotting.

†English controls.

Urinalysis in three clinically envenomed patients showed the abnormalities noted in Patient 5, and proteinuria in Patient 2. Haemoglobinuria was not present in either of these other two patients. In none of the patients was there evidence of significant intravascular haemolysis or rhabdomyolysis.

Haemostasis

Four patients were studied but, unfortunately in two, pre-antivenom samples were not taken (Table 3). Initially, prothrombin and activated partial thromboplastin times were prolonged in three patients; the fibrinogen level was reduced in one patient and at the lower limit of normal in two others, rising during admission. There were decreases in a number of coagulation factors (Table 3), most noticeably Factor V, VIII, XIIIa, anti-thrombin III and protein C, and levels of thrombin-antithrombin complex were elevated.

FDP levels were mildly elevated in three of the four patients and both plasminogen and α_2 antiplasmin levels were slightly decreased in two patients.

DISCUSSION

We have described nine patients proved by EIA to have been bitten by Papuan black snakes. Seven of them showed clinical evidence of envenoming including neurotoxicity and haemostatic disorders, but in the other two, in whom venom antigen was detectable in the serum by EIA (Table 2), there were no objective clinical signs of envenoming. Since the EIA test antiserum is raised against whole venom, it is likely that, in these two patients,

non-toxic species-specific venom components were being detected by EIA but that insufficient toxic venom components had been injected to cause clinical envenoming. The only other report of bites by *P. papuanus* was by CAMPBELL (1967), but in only two of his patients could envenoming by this species be proved (CAMPBELL, 1967; C. H. CAMPBELL, personal communication, 1992). A 25-year-old man (Case number 28643 in Table 1 in CAMPBELL, 1967) was bitten on the dorsum of the right hand while capturing a 5 foot long specimen which was later identified by the late Eric Worrell, a distinguished herpetologist. His hand became swollen and painful, he vomited several times and developed tender lymph glands in his right axilla. He was treated with 36,000 units of Papuan black snake antivenom 3 hr after the bite. No neurotoxic signs developed and bleeding and clotting times, fibrinogen titre and platelet count remained normal, although the rabbit anti-fibrin test (for fibrin degradation products) was positive. A 30-year-old man was bitten on the left index finger by an 18 inch long *P. papuanus* (Case number 4252, C. H. CAMPBELL, personal communication, 1992). He developed tender enlargement of left axillary lymph nodes and vomited. Five and a half hours after the bite he was treated with 9000 units of Papuan black snake antivenom and 9000 units of tiger snake antivenom. Later, he developed upper abdominal pain, pain in the bitten arm and minimal bilateral ptosis.

The clinical features in these two cases were entirely consistent with those in our group of nine patients, which confirm that envenoming by *P. papuanus* is capable of producing life-threatening paralytic symptoms in humans as has been shown in animals (CAMPBELL, 1976; KAMIGUTI *et al.*, 1994). It seems likely that the high phospholipase activity of *P. papuanus* venom (DOERY and PEARSON, 1961; KAMIGUTI *et al.*, 1994) may be responsible, as in the case of venoms of the red-bellied or common Australian black snake (*P. porphyriacus*) (VAUGHAN *et al.*, 1981) and *P. colletii* (WEINSTEIN *et al.*, 1992), which is thought to be closely related to *P. papuanus* (MENGDEN *et al.*, 1986). There was a clinical impression that, compared with taipan envenoming, neurotoxicity was less severe in the *P. papuanus* victims and that it resolved more quickly after antivenom treatment. Even though *P. papuanus* venom is no longer used in the production of Commonwealth Serum Laboratories antivenom (THEAKSTON and WARRELL, 1991), the accompanying paper (KAMIGUTI *et al.*, 1994) confirms the efficacy of CSL polyvalent Australia–Papua New Guinea antivenom in experimental animals.

Haemostatic disturbances in our patients with proven *P. papuanus* envenoming included spontaneous systemic bleeding, prolongation of prothrombin time and APTT, mild depletion of fibrinogen, mild thrombocytopenia and a moderate decrease in many other haemostatic factors (Table 3). Increased levels of fibrin(ogen) degradation products and slight decreases in plasminogen and α_2 antiplasmin level indicate increased fibrinolytic activity. The elevated levels of thrombin–antithrombin complexes suggest that generation of thrombin may have caused many of the observed clotting factor deficiencies. These observations are consistent with the demonstration in laboratory studies of haemorrhagic, mild procoagulant and powerful anti-platelet or anticoagulant activity (KAIRE, 1964; CAMPBELL and CHESTERMAN, 1972; MARSHALL and HERMANN, 1983, 1989; KAMIGUTI *et al.*, 1994).

Non-clotting blood in the WBCT20 is usually associated with marked fibrinogen depletion, but in the presence of powerful anti-platelet or anticoagulant activity blood may not clot in 20 min, even though the levels of clotting factors are adequate. It is interesting that the blood of two of our patients (Patients 1 and 2) was said to be incoagulable when they were first seen by medical staff.

Bleeding which occurred for the first time 48 hr after the bite in Patient 5 is uncommon in our experience with other Australasian elapids. Clotting tests at the time of this bleeding episode were all normal, although this patient did have a reduced platelet count (Table 3) and was mildly uraemic. However, of particular interest is the fact that this patient had not received an appropriate specific antivenom. It is therefore likely that venom components were circulating for much longer than is usual in patients treated with specific antivenom and that this late bleeding arose from a combination of persisting haemorrhagin and anti-platelet and anticoagulant activity.

Renal impairment, observed in Patient 5, has not previously been associated with bites by this species, but the syndrome is well recognised in bites by the closely related king brown or mulga snake (*P. australis*) and other Australasian elapids (SUTHERLAND, 1983). The mechanism in other Australasian species remains unclear, but direct nephrotoxicity of the venom, myoglobinuria and disseminated intravascular coagulopathy have been implicated (WHITE and FASSETT, 1983; BRIDGEN and SUTHERLAND, 1981; ACOTT, 1988).

Some of the 13 patients with suspected *P. papuanus* envenoming described by CAMPBELL (1967) were defibrinogenated and had 'haemoglobinuria' indicating intravascular haemolysis. We think it more likely that these patients had been bitten by taipans (LALLOO *et al.*, 1992) and that the 'haemoglobinuria' may have reflected spontaneous bleeding into the urinary tract or possibly myoglobinuria which cannot be distinguished by dipstick testing.

Campbell's studies suggested that *P. papuanus* used to be the predominant biting species in the Port Moresby area (CAMPBELL, 1967). Slater, who collected snakes in the 1950s, regarded *P. papuanus* as the most common venomous snake in the region; it was especially common on the coast to the east of Port Moresby (K. R. SLATER, personal communication to C. H. CAMPBELL). However, after 1969 it could not be collected as a source of venom for antivenom production (WHITAKER *et al.*, 1982). As far as we know, in the last 20 years, only two adult live specimens have been caught in the country, both in the Western Province (H. KRATZER, M. O'SHEA, personal communications). We were sent three dead specimens, two from Veifa'a, in the northwest of Central Province and one from Moreguina in the east, in 1992-3 (Figs 1-4). Attempts over several months by a herpetologist associated with our project failed to find any other live or dead specimens in Central Province. This decline in Papua New Guinea's most notorious snake may have resulted from the introduction and spread of the American cane toad (*Bufo marinus*) throughout much of Central Province since its introduction from Rabaul in the 1940s (J. MENZIES, personal communication; CURRIE *et al.*, 1988). It was also introduced to Australia from the Americas via Hawaii in 1935 in an attempt to reduce the destruction of sugar cane crops by larvae of the grey back and Frenchi beetles. In Australia *B. marinus* has caused a decline in number of indigenous vertebrates, including the snakes *P. porphyriacus*, *Acanthophis antarcticus* and *Pseudonaja textilis*, probably by eating their young and by poisoning snakes which attempted to eat them (COVACEVICH and ARCHER, 1975).

Campbell may have overestimated the importance of *P. papuanus* because, in the majority of cases, he had to rely on patients' descriptions of the biting snake which we regard as unreliable. It seems likely that taipans were responsible for some of these bites. EIA has allowed us to define the clinical and laboratory features of *P. papuanus* envenoming. Further studies should assess the clinical efficacy of antivenom and the pathophysiology of coagulopathy and neurotoxicity.

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