CONSUMPTIVE COAGULOPATHY CAUSED BY A BOOMSLANG BITE*

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In South Africa there are 3 groups of poisonous snakes. They can be divided into the erectile fanged, the front fanged and the back fanged.

The boomslang (*Dispholidus typus*) belongs to the back-fanged group; it is generally non-aggressive and bites are uncommon. A total of 23 cases of proved or presumed bites by the boomslang are known to us. Some of these have been reported in the medical or herpetological literature,[1-3] and details of other cases of boomslang bite were supplied by Dr P. A. Christensen of the South African Institute for Medical Research. Seventeen of the patients received no specific treatment and 5 of them died.

A limited amount of freeze-dried specific boomslang antivenom was prepared in 1964 by the SAIMR, and 4 patients with proved boomslang bites and 2 with presumed boomslang bites have been treated with this serum. All survived. One of these patients, whose bite was undoubtedly caused by a boomslang, was treated at Johannesburg Hospital. Investigations carried out on him gave some insight into the nature of the venom's action and demonstrated the efficacy of the specific antivenom.

CASE REPORT

A 26-year-old carpenter, who works in the Kruger National Park and keeps snakes as pets, was admitted to Johannesburg Hospital on 2 August 1968, having been bitten by his pet boomslang 31 hours previously. One of the snake's fangs had penetrated the tissue at the base of the nail of his right index finger. The patient had tied a tourniquet round his wrist, had cut into the wound with a scalpel blade and had attempted to milk out the venom. Immediately after the incident he developed pain in the index finger, over the dorsum of the hand and down the inner aspect of the arm.

Fourteen hours after the patient had been bitten he left the Park and drove with a friend to his parents' home some 150 miles away. During the journey he developed nausea and started vomiting. By the time he reached his home he had vomited 5 or 6 times; initially the vomitus was dark in colour and later became bright red. While travelling he also noticed that a fever blister on his lip had become swollen and had started to bleed and that his gums had started to bleed spontaneously. Twenty-two hours after the bite he first noticed blood in his urine. By the time he reached his parents' home, severe abdominal cramps had started to develop. He then contacted his private practitioner, who immediately referred him to hospital.

On systematic enquiry it was found that an occipital headache had been present for 12 hours. In addition, he had coughed up approximately a quarter of a cupful of blood. There was no history of melaena. Past history was non-contributory, apart from the fact that he had had spinal poliomyelitis as a child. As a result of the kyphoscoliotic deformity he was dyspnoeic on effort. There was no previous history of any bleeding disorder, either in the patient or in his family.

Examination revealed a young man, mildly dyspnoeic but in no real distress. There was no pallor, cyanosis or jaundice. He had a marked thoracic kyphoscoliosis. He was bleeding from a fever blister on his lip, but there was no other evidence of haemorrhage into the skin. The blood pressure was 180/90 mm.Hg and the pulse rate 90/min. The physical examination was otherwise non-contributory. At the time of admission occult blood was present in the faeces, and the patient was oliguric and had macroscopic haematuria.

Laboratory Investigations

The haemoglobin was 18·1 G/100 ml.; the white cell count was 12,900/cu.mm. and the platelet count was 10,000/cu.mm. The bleeding time (Ivy method) was 20 minutes. The blood failed to clot in the Lee-White test for clotting time. In Quick's one-stage test for prothrombin time the blood also failed to clot. Plasma fibrinogen (Ellis and Stransky method) was 10 mg./100 ml. The euglobulin lysis time was normal and the Schumm's test was positive. The spectroscopic test for methaemoglobin was positive, the partial thromboplastin time was abnormal, and the Coombs test was negative. The blood urea was 86 mg./100 ml., serum electrolytes were normal and serum bilirubin was 1·2 mg./100 ml. (direct 0·4 mg./100 ml.).

Progress

At this stage specific boomslang antivenom, which was obtained through the courtesy of the SAIMR, was administered intravenously after an intracutaneous test dose had been given with no adverse effect. During the injection of the contents of the first ampoule the patient developed rigors and severe dyspnoea. Two hundred mg. hydrocortisone were given intravenously as a bolus and a further 300 mg. hydrocortisone were given in 150 ml. of 5% dextrose water by slow intravenous infusion, with good response. The contents of a second ampoule of antivenom were then dissolved in 150 ml. of 5% dextrose water and given intravenously over a period of 2 hours. At the same time, 50 mg. mepyramine were given in 150 ml. of 5% dextrose water. The contents of a third and fourth ampoule of antivenom were given in a similar manner over the following 12 hours.

On this therapy the platelet level remained at 10,000/cu.mm. for the first 24 hours and then rose to 300,000/cu.mm. within 7 days. Other clotting tests showed a progressive improvement to normal over the first 72 hours (Figs. 1 and 2). However, during this period the haemoglobin dropped progressively. On the day after admission the haemoglobin level was still 17·5 G/100 ml., but it fell over the next 4 days to 7·4 G/100 ml., at which level it stabilized. Blood smears showed marked morphological changes, with evidence of anisocytosis, poikilocytosis, spherocytosis, macrocytosis, schistocytosis and punctate basophilia (Fig. 3). There was toxic granulation of the white blood cells. Over the same period there was a rapid rise in the levels of the bilirubin and serum enzymes. The

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total bilirubin was 44 mg./100 ml. on the third day, with direct value of 24 mg./100 ml. By the tenth day these figures had again dropped to the normal levels which had been recorded on admission.

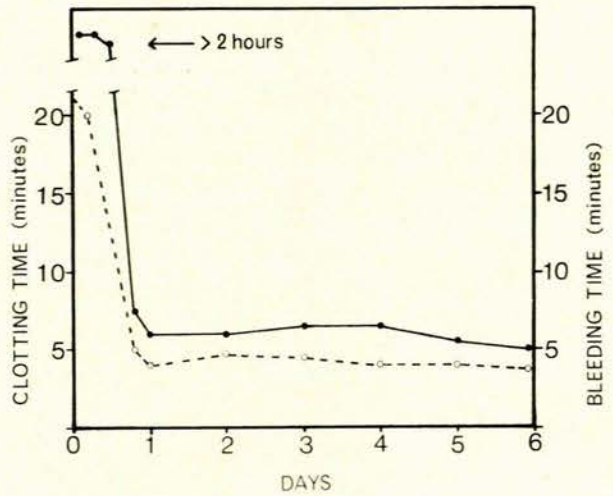

Fig. 1. Bleeding time (o - o) and clotting time (● - ●), showing return to normal within the first 24 hours.

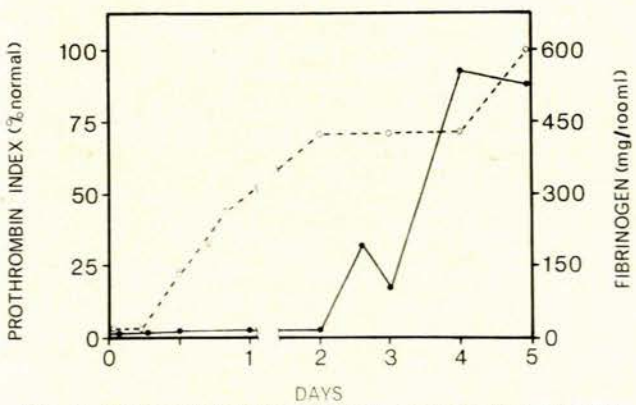

Fig. 2. Prothrombin index (percentage normal o - o) and fibrinogen (mg./100 ml. ● - ●) showing a gradual return to normal following the administration of specific boomslang antivenom.

Initially, occult blood was present in the patient's stool. This soon disappeared, but diarrhoea persisted for several more days. Shortly after admission he passed 50 ml. murky, grey urine containing methaemoglobin. Severe oliguria continued over the next 3 days, by which time the blood urea had reached a level of 386 mg./100 ml. The rapidly rising urea, virtual anuria and the fact that the patient's gross deformity excluded peritoneal dialysis were considered to be indications for haemodialysis. A Scribner shunt was therefore inserted and haemodialysis on a twin-coil Kolff unit was carried out over a period of 6 hours. On the sixth day in hospital the blood urea had again risen to above 300 mg./100 ml. and a second haemodialysis was performed. This was repeated on the ninth day and, finally, on the thirteenth day after admission to the hospital. Just before the last dialysis a biopsy specimen was obtained by a semi-open procedure, to ascertain whether the pathology was primarily cortical or in the medulla. This revealed the presence of haemoglobinuric nephrosis and tubular necrosis (Fig. 4), and a large arteriole was noted in the biopsy specimen.

Following biopsy the patient passed 1,200 ml. clotted blood *per urethram*. This was shown to have the same urea and electrolyte concentration as the plasma. He was transfused with 2 pints of packed cells. From the 15th day there was a progressive rise in the urinary output,

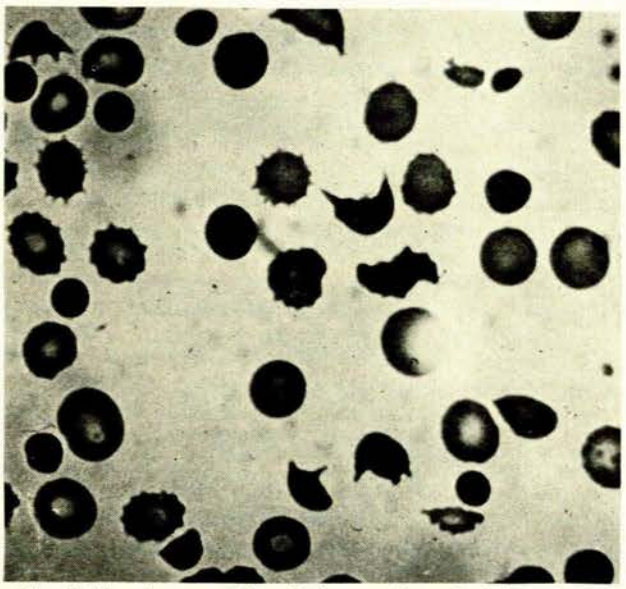

Fig. 3. Blood smear taken 12 hours after admission, showing evidence of a microangiopathic haemolytic anaemia, i.e. anisocytosis, fragmented cells, burr cells, spherocytosis and macrocytosis.

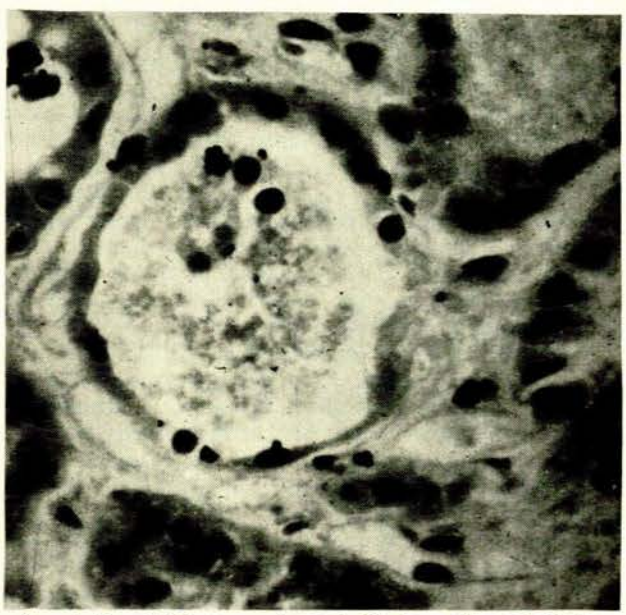

Fig. 4. Renal biopsy performed 12 days after admission, showing the presence of haemoglobin casts, tubular necrosis and marked interstitial oedema.

and the amount of blood passed in the urine gradually diminished. At the same time the level of blood urea began to fall. However, he remained anaemic and a further transfusion of 2 pints of blood was given on the 28th day.

Subsequent progress was uneventful and the patient was discharged 48 days after admission. At this time the haemoglobin level was 14·7 G/100 ml., the blood urea 28 mg./100 ml., serum electrolyte levels were all within normal limits and the total serum bilirubin was 1·1 mg./100 ml. (direct bilirubin 0·3 mg./100 ml.).

DISCUSSION

Owing to the relative rarity of boomslang bites, very little is known about the mode of action of the venom. Previous authors have noticed haemolysis and have attributed this to a haemolysin contained in the venom.[9] Evidence has also been produced to suggest that the venom contains a proteolytic enzyme which causes increased capillary permeability and hence extravasation of blood.[3]

A clearer understanding of the venom's mode of action was obtained in the present patient. The clotting defects manifested during the early part of his illness (viz. markedly prolonged bleeding and clotting times, prolonged prothrombin time, low platelet count, decreased fibrinogen, abnormal thromboplastin generation and a normal euglobulin lysis time) were all consistent with a diagnosis of consumptive coagulopathy. Although fibrin thrombi were not detected in the renal biopsy specimen, this does not exclude disseminated fibrin deposition. In animals, for example, where intravascular coagulation has been induced experimentally, pulmonary artery clots have often not been demonstrable.[10] This may be due to activation of the fibrinolytic system[11] with consequent lysis of the clots, or to binding of fibrin by the reticulo-endothelial system.[12,13]

In this context it is worthy of mention that necropsy examination of a previous patient who died following a boomslang bite, revealed diffuse fibrin thrombi in the brain, liver and lungs, but sections of the kidney showed only the presence of haemoglobin in the tubules.[6] Boomslang bite can therefore be added to the growing list of conditions which have been described in association with this recently recognized clotting abnormality. These include a wide range of medical, surgical, gynaecological and obstetric conditions which lead to disseminated intravascular coagulation. As a result, the levels of a number of clotting factors and of platelets are reduced, so that various bleeding manifestations may occur.

The present findings supplement those of workers who have investigated the effects of other snake venoms. Certain snake venoms are known to cause defibrination.[14-16] In particular it has recently been shown that the Malayan pit viper venom contains a potent anticoagulant which causes rapid and marked defibrination, but only a transient decrease in the platelet count.[14,15,17-19] It is, however, doubtful whether boomslang venom acts in the same way, since the findings in the present patient and in the case reported by Spies *et al.*[6] indicated a marked consumption of platelets and of other clotting factors, suggesting that this venom acts at a different level of the clotting mechanism and probably as an activator of thromboplastin formation.

Other actions have been ascribed to the venoms of a number of snakes. Both direct (direct lytic factor—DLF) and indirect (phospholipase A) haemolysins have been demonstrated and some of these venoms have been shown to cause variable amounts of haemolysis *in vitro*. However, *in vivo* haemolysis has been found to be temporary and evanescent. Furthermore, there are powerful defibrinating venoms which cause haemolysis *in vivo*, but which have no haemolytic effects *in vitro*. These venoms do not contain a specific haemolytic factor, but probably cause haemolysis *in vivo* on the basis of defibrination. The fact that boomslang venom is at most feebly haemolytic when incubated *in vitro* with red blood cells from sheep[9] or guinea-pigs, even in the presence of lecithine,[3] does not exclude the possibility that it may cause haemolysis *in vivo*.

It seems likely that the major cause of haemolysis in our patient was microangiopathic red cell damage consequent on widespread intravascular coagulation. The mechanisms involved in the production of haemolysis and red cell fragmentation under such circumstances have recently been studied in animals by the intravenous injection of 'Arvin', the purified coagulant fraction of Malayan pit viper venom,[20] and *in vitro* by defibrination with glass beads.[21] The findings suggest that two major factors are required for the production of microangiopathic haemolytic anaemia. These include rapidly flowing blood and the presence of fibrin strands which obstruct the passage of red cells. The firm adherence of a small area of the red cell membrane to a fixed fibrin strand on the endothelium or at the periphery of a microthrombus results in distortion and tearing of the red cell membrane. Such a mechanism accounts both for the release of haemoglobin and for the formation of the red cell fragments. The process tends to be self-perpetuating, since rupture of red blood cells leads to the release of thromboplastic substances from the membranes. Such an interpretation would certainly account for the anaemia, red cell fragmentation, haemoglobinaemia and haemoglobinuria which were observed in our patient.

The renal involvement was probably solely due to haemoglobinuric nephrosis, since no cortical involvement was seen. In the classical Schwartzmann phenomenon, the cortex and not the medulla of the kidney is usually involved.

As has been noted, the bilirubin rose to a level of 40 mg./100 ml. A large proportion of the bilirubin was unconjugated and could be accounted for on the basis of the haemolytic anaemia. However, a significant amount of direct reacting bilirubin was also present and the possibility that this was due to the presence of fibrin thrombi, or that the venom has a direct hepatotoxic effect, cannot be excluded.

Treatment in our patient was initially directed towards neutralizing the boomslang venom with the specific antivenom. Prednisolone was added only after the patient developed a pyrogenic reaction to the antivenom. The subsequent course of our patient may have been worsened by this therapy, since Margaretten[22] has shown that prednisolone can aggravate disseminated intravascular coagulation and haemolysis. Subsequent therapy was aimed at correcting the renal failure. It is possible that the renal and other complications could have been diminished by the use of heparin to break the vicious cycle of repeated intravascu-

lar coagulation. Heparin acts predominantly at the level of conversion of prothrombin to thrombin,[23] and it is ineffective in counteracting the Malayan pit viper venom, which acts on the conversion of fibrinogen to fibrin which boomslang venom does not do.[24]

Its administration in cases of boomslang bite might nevertheless be expected to be beneficial, since the venom appears to act as an activator of the thromboplastin mechanism. It should, however, be noted that heparin alone fails to protect mice against the effect of boomslang venom,[25] and if it is to be used in man it should be given together with the specific antivenom.

SUMMARY

A case of disseminated intravascular coagulation resulting from a boomslang bite is presented, and the possible mechanisms involved in the pathogenesis of this disorder are discussed.

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ADDENDUM

Subsequent to submission of the above article for publication, it has been brought to our notice that a further case of successful treatment and reversal of clotting abnormalities by the administration of specific antivenom has been reported.[26]

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