it also seems desirable to limit the dose of α-methyl-
dopa to less than 2 grammes per day. In our clinic
several drugs are used in combination to minimize the
side effects of each (Doyle, 1966). If this type of régime
is used doses of α-methyl-dopa larger than 2 grammes per
day are seldom needed. Finally, it should be remembered
that follow-up of the hypertensive patient does not merely
involve inquiry about his well-being and taking his blood
pressure, but requires considerable attention to detail.
Periodic checks of cardiovascular and renal functions are
essential. As well as this, one must be on the look out
for the development of gout, skin rashes, depression and
other side effects of hypotensive therapy. The patient on
α-methyl-dopa therapy should be observed carefully for
the development of anemia, as hemolysis in these patients
is usually not acute in onset but mild and insidious,
and therefore amenable to diagnosis before severe anemia
and complications have developed.

SUMMARY
In a series of 80 patients treated with α-methyl-dopa
the incidence of positive reactions to the direct Coombs
test was 14%. The incidence was dose-dependent, being
25% in those taking more than 750 mg. a day of the drug.
There was no evidence of anemia or hemolysis in this
group of patients. Examination of the patients with
hemolytic anemia giving positive results to the Coombs
test who were seen at the Royal Melbourne Hosptial since
1961 revealed that two patients were taking α-methyl-dopa
when their anemia presented.

ACKNOWLEDGEMENTS
We are indebted to the staff of the Clinical Pathology
Department at the Royal Melbourne Hospital who per-
formed the serological investigations, and to the staff of
the Biochemistry Department at the Royal Melbourne
Hospital for their assistance.

We are also indebted to the staff of the Royal Melbourne
Hospital for permission to search the past records, and
to Merck Sharp and Dohme International Research for
their assistance.

REFERENCES
"Methyldopa and Acquired Haemolytic Anaemia", Med. J.
Aust., 2: 760.

Carr, D. A. (1966), "Methyldopa and Haemolytic Anaemia",

Carstairs, K. C., Breckenridge, A., Dollery, C. T., and
Worledge, S. (1966), "Incidence of a Positive Direct
Coombs Test in Patients on α-Methyl Dopa", Lancet,
2: 133.

Carstairs, K. C., Worledge, S., Dollery, C. T., and
Breckenridge, A. (1966), "Methyldopa and Haemolytic Anaemia",

Day, M. D., and Rand, M. J. (1963), "Hypothosis for Mode
of Action of α-Methyl-Dopa in Relieving Hypertension", J.
Pharm. Pharmac., 15: 221.

Doyle, A. E. (1965), "Advances in the Treatment of High

Worledge, S., Carstairs, K. C., and Dacie, J. V. (1966),
"Autoimmune Haemolytic Anaemia Associated with α-Methyl-

ANTIVENENE IN THE TREATMENT OF AUSTRALIAN AND
PAPUAN SNAKE BITE

Port Moresby General Hospital, Papua

In 1896 Calmette produced the first commercially available
antivenene for the treatment of snake bite, prepared
by injecting horses with a venom mixture containing 80%
cobra venom. Calmette (1894 a, b, c; 1895) claimed that
the antivenene would be effective against all forms of
snake-poisoning.

This claim was disputed by Kanthack (1896) who said it
was contrary to Behring's law of serum specificity, and
was soon proved to be wrong by Martin (1897 a) and
Tidswell (1906) in Australia, who showed that Calm-ette's
serum did not protect animals against Australian tiger
snake, black snake, brown snake and death adder venoms.
Martin (1897 b; 1898) further proved that the subcutaneous
dose of antivenene had to be 10 to 20 times the intravenous
dose, and recommended that the intravenous route only be
used in treating snake-bite cases. It is also of interest
to note that as early as February, 1893, while others in
Australia were preoccupied with the merits of strychnine
as a cure for snake bite, Baneroff thought that the serum
of animals immunized against snake venom "might prove
useful as a remedy in snake bite".

In 1901 the first specific antivenene to be produced in
quantities was prepared by Tidswell (1902, 1906), working
in the laboratories of the N.S.W. Department of Health.
Tidswell produced a specific tiger snake antivenene which
he had prepared by cautiously immunizing a horse over
a period of three years with tiger snake venom. He showed that
this antivenene was ineffective against other venoms,
and was uncertain as to what role it would eventually play in therapeutics.

Lamb in India (1903, 1904a, 1904b, 1905) produced
specific cobra and daboia antivenenes and confirmed

1 Formerly Specialist Medical Officer (Physician), T.P.N.G.;
present address, School of Public Health and Tropical Medicine,
University of Sydney.

Tidswell's findings that antivenenes were specific in their
action, effective only against the venom with which they
had been prepared. Later work showed that antivenenes
may have some protective action against the venoms of
species of snakes other than the one used for their pre-
paration and that their action, while being highly specific,
was not entirely so (Houssay and Negrete, 1952; Velliar,
1950).

After the important early work of Martin and Tidswell
on snake venoms and antivenenes in Australia, interest
waned until 1927 when the late Sir Neil Hamilton Fairley
(1929), after his return to Australia, interested the Director
of the Walter and Eliza Hall Institute, Dr. C. H. Kelloway,
in the study of Australian poisonous snakes and their
venoms. Through Dr. Kelloway, Dr. F. G. Morgan, the
Director of the Commonwealth Serum Laboratories, was
interested in the production of antivenene, and he comm-
enced work with the object of producing tiger snake,
copperhead and death adder antivenenes in July, 1929.

Tiger snake antivenene became generally available in
Australia towards the end of 1929 and it proved to be a
highly effective antivenene and to give some cross
protection against the venom of the Australian copperhead
snake, and was subsequently recommended for use in the
treatment of death adder bites, brown snake, black snake
and mulga snake bites. Difficulty in producing an effective
dehth adder antivenene was experienced for many years
(Morgan, 1929; 1933), and it did not become available
commercially until 1955. Specific taipan antivenene
and specific Papuan black snake antivenene were produced
in 1955 and 1958. In 1962, the first Australian polyclonal
antivenene was prepared for use in treating snake bite in
Papua and New Guinea.

The Australian venomous land snakes all belong to the
class Elapidae. The lethal factor of these venoms is the
neurotoxin which produces a peripheral neuromuscular block (Kellaway and Diffi, 1952), causing a generalized flaccid muscle paralysis. Respiratory paralysis is produced by paralysis of the jaw and tongue, or by the accumulation of secretions in the pharynx and bronchi. The obstruction to respiration aggravates the respiratory insufficiency caused by weakness of the muscles of the chest and diaphragm. The victim dies of asphyxia. Some venoms also contain a thrombolytic, which produces intravascular coagulation and a secondary fibrinogenopenia. Venoms may also contain a hemolytic which may lead to hemoglobinuria.

Other toxic factors in the elapid venoms are of little clinical importance. After a venomous snake bite no symptoms may occur, mild, moderate or severe symptoms and signs may be produced with eventual recovery, or death may result. The outcome in untreated cases depends on the dose of venom injected relative to the size of the victim.

Because the amount of venom injected by a snake is quite variable, the clinical evaluation of the effectiveness of antivenin in the prevention of the symptoms and signs of envenomation following a venomous snake bite is very difficult. In fact, it is impossible to know in a particular case whether antivenin has been of value in preventing serious envenomation or not. Hence isolated case reports, claiming antivenin to be of value in the prevention of snakebite envenomation, are of little value.

While clinically there may be doubt about the effectiveness of elapid antivenines in preventing the serious symptoms and signs of envenomation, there should be no doubt about the effectiveness of elapid antivenines in the treatment of established snake-poisoning. "For nothing is more dramatic in the whole range of specific therapy than the effects of intravenous antivenin in badly paralysed cases bitten by cobra, krait, and elapid snakes" (Fairley, 1933). The bad paralysis is dramatically cured or reversed by the antivenine. An antivenine which is effective in reversing the effects of the venom would also be effective in preventing signs and symptoms of snake-poisoning.

Cobra antivenine was shown by Arthus (1919) in experiments on rabbits to reverse, over a period of two to six hours, the paralysis of the diaphragm produced by cobra venom, and clinical experience in India (Fairley, 1933; Mackie, 1933; Abuja and Singh, 1954) and elsewhere (Puranamanna, 1956), have confirmed its effectiveness in treating established cobra envenomation.

Kellaway (1952), however, was unable to reverse to any significant extent with specific antivenine the muscle paralysis produced by cobra venom in rabbits, and despite the availability of antivenines in Australia for over 30 years, there is little published evidence of their effectiveness in treating human cases of snake bite. Bill (1902) was the first to use snake antivenine in Australia and claimed it was of value, although he used Calmette's antivenine and this had previously been shown to be valueless in the treatment of Australian snake-poisoning.

Tisdall and Sewell (1931) published the first report of a case of snake bite in which tiger snake antivenine was used in Australia, and claimed that it had saved life. Their patient only had a partial paralysis when seen 24 hours after the bite, and the recovery rate of the paralysis following the use of the antivenine was not accelerated. Lloyd (1932) treated three patients with tiger snake antivenine, and stated that it was effective in saving life in one case, even though no symptoms of snake-poisoning were evident in this patient. Morgan (1953) also said that he knew of 14 cases in which tiger snake antivenine had been used and "life had been saved by its use in some seriously ill cases. No details of the cases were given, so it is difficult to evaluate his assertion.

Tiger snake antivenine was used by Reid and Flecker (1959) in the treatment of a patient bitten by a taipan, and was said to have contributed to the recovery of the patient, but to have been of no value in another case of taipan bite reported by Benn (1951). Lester (1954) reported the first case of a taipan bite treated with specific taipan antivenine and considered that improvement commenced after the injection of the antivenine, but no dramatic reversal of the paralysis took place. Indeed, before 1966 there was only one case of snake bite in the Australian medical literature in which a dramatic reversal of the paralysis has occurred after antivenene administration. In 1959, Knyvet and Molony reported the complete disappearance of all signs 10 hours after the use of 12,000 units of taipan antivenine in the treatment of a seriously paralysed patient bitten by an unknown snake. Previously the paralysis had progressed to a stage where artificial respiration was required despite the use of 33,000 units of tiger snake antivenine.

In Papua there are three highly venomous snakes—the death adder (Acanthophis antarcticus Shaw), the taipan (Oxyuranus scutellatus cani Slater), and the Papuan black snake (Pseudechis papuanus Peters and Doria). Specific antivenenes are available for the treatment of bites by these snakes and there is in addition a Papuan polyvalent antivenene available.

Early experience with the antivenene therapy of snake bite at the Port Moresby General Hospital was disappointing (Campbell and Young, 1961; Campbell, 1964). This evaluation of antivenene therapy was primarily concerned with its effectiveness in preventing and treating the effects of the neuromuscular toxins in the venoms. The effect of the antivenine on other toxic factors in the venom was not assessed, though hemoglobinuria had been noted to cease shortly after the administration of antivenenes (Campbell and Young, 1961) and the blood was noted to clot normally in wounds 24 to 48 hours after admission.

If injected early, antivenenes were considered to be of value in preventing paralysis. When used after significant paralysis was present, the antivenene never reversed the paralysis, which often would have progressed to a fatal issue if a tracheotomy had not been performed and artificial respiration carried out. However, two patients did show rapid improvement of their only sign of paresis, after the injection of antivenene (Campbell, 1964). (In retrospect, both patients were probably bitten by death adders.)

PRESENT STUDY

At the Port Moresby General Hospital from March, 1964 until November, 1965, 28 patients with symptoms and signs of snake-poisoning were given intravenous injections of antivenene. The relevant clinical details are summarized in Table 1. Five of these patients had also received antivenene three to 17 hours previously at an outstation. If the species of snake inflicting the bite was known with a reasonable degree of certainty, specific antivenene was injected. More commonly, polyvalent antivenene was given. The usual dose of antivenene was twice the recommended dose (115 cases). The recommended dose is calculated to neutralize the average venom yield of a bite, and in only three patients received this dose. Three patients received three times the recommended dose; four, four times the recommended dose; and two, five times the recommended dose. The method of injecting the antivenene intravenously has been reported previously (Campbell, 1963). No tests for serum sensitivity were performed. The term "probable death" is used when it was thought that death would have resulted had there not been a tracheotomy or a tracheotomy and artificial respiration been carried out.

RESULTS

Death Adder

The only patients to have their paralysis reversed by antivenene were those bitten by death adders. New Guinea polyvenal and death adder antivenenes (doses used—two, three and five times the recommended dose) were highly effective antivenenes, at least up until seven hours after the bite, reversing within two or more hours of the injection the serious effects of death adder bites.

Taipan

In the patient with serious paralysis (two doses of polyvenal and one dose of taipan antivenene having previously been given on the outstation), the paralysis was not reversed by polyvalent antivenene (twice the recommended
<table>
<thead>
<tr>
<th>Type of Bite</th>
<th>Hospital Number</th>
<th>Sex</th>
<th>Approximate Age (Years)</th>
<th>Hours Between Bite and Antivenene</th>
<th>Condition when Antivenene Given</th>
<th>Progress after Antivenene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death adder</td>
<td>27353</td>
<td>M.</td>
<td>25</td>
<td>4 (1 at out-station)</td>
<td>Early signs — no symptoms</td>
<td>No change*</td>
</tr>
<tr>
<td></td>
<td>28488</td>
<td>M.</td>
<td>29</td>
<td></td>
<td>Extensive paralysis</td>
<td>Paralysis reversed</td>
</tr>
<tr>
<td></td>
<td>35645</td>
<td>M.</td>
<td>33</td>
<td>7</td>
<td>Early signs and symptoms*</td>
<td>Paralysis reversed</td>
</tr>
<tr>
<td></td>
<td>58844</td>
<td>M.</td>
<td>35</td>
<td>6</td>
<td>Early signs and symptoms, slight paralysis</td>
<td>Paralysis reversed</td>
</tr>
<tr>
<td></td>
<td>82059</td>
<td>F.</td>
<td>35</td>
<td>4-5</td>
<td>Extensive paralysis</td>
<td>No progression</td>
</tr>
<tr>
<td>Talpan</td>
<td>30447</td>
<td>M.</td>
<td>40</td>
<td>2-5</td>
<td>Early signs and symptoms, inconaguable blood, hemorrhodiumuria</td>
<td>No progression</td>
</tr>
<tr>
<td></td>
<td>31512</td>
<td>F.</td>
<td>30</td>
<td>2-5</td>
<td>Moderate paralysis</td>
<td>Progress to probable death</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(4 at out-station)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papuan black snake</td>
<td>24281</td>
<td>M.</td>
<td>30</td>
<td>4</td>
<td>Severe early signs and symptoms, No paralysis, inconaguable blood, hemorrhodiumuria</td>
<td>Progress to slight paralysis</td>
</tr>
<tr>
<td></td>
<td>26061</td>
<td>M.</td>
<td>45</td>
<td>45</td>
<td>Extensive paralysis</td>
<td>No change</td>
</tr>
<tr>
<td></td>
<td>26463</td>
<td>M.</td>
<td>25</td>
<td>3</td>
<td>Early signs and symptoms, No paralysis</td>
<td>No progression</td>
</tr>
<tr>
<td></td>
<td>29314</td>
<td>M.</td>
<td>8</td>
<td>8</td>
<td>Extensive paralysis</td>
<td>Progress to probable death</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(4-5 at out-station)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30058</td>
<td>F.</td>
<td>55</td>
<td>61</td>
<td>Extensive paralysis</td>
<td>Died</td>
</tr>
<tr>
<td></td>
<td>25580</td>
<td>M.</td>
<td>15</td>
<td>1</td>
<td>No progression</td>
<td></td>
</tr>
<tr>
<td></td>
<td>27130</td>
<td>M.</td>
<td>30</td>
<td>5</td>
<td>Early signs and symptoms, slight paralysis</td>
<td>No progression</td>
</tr>
<tr>
<td></td>
<td>28965</td>
<td>M.</td>
<td>25</td>
<td>4-5</td>
<td>Early signs and symptoms, inconaguable blood, hemorrhodiumuria present</td>
<td>No progression</td>
</tr>
<tr>
<td></td>
<td>35302</td>
<td>M.</td>
<td>25</td>
<td>3</td>
<td>Early signs and symptoms, inconaguable blood, hemorrhodiumuria present</td>
<td>No progression</td>
</tr>
<tr>
<td></td>
<td>33122</td>
<td>M.</td>
<td>40</td>
<td>2-5</td>
<td>Slight paralysis, hemorrhodiumuria</td>
<td>No change</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(20 at out-station)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30051</td>
<td>F.</td>
<td>25</td>
<td>6</td>
<td>Slight paralysis, inconaguable blood, hemorrhodiumuria</td>
<td>Progress to probable death</td>
</tr>
<tr>
<td></td>
<td>30101</td>
<td>F.</td>
<td>30</td>
<td>14</td>
<td>Slight paralysis</td>
<td>Slight progression</td>
</tr>
<tr>
<td></td>
<td>31409</td>
<td>M.</td>
<td>10</td>
<td>5</td>
<td>Severe early signs and symptoms, no paralysis</td>
<td>Progress to probable death</td>
</tr>
<tr>
<td></td>
<td>31853</td>
<td>M.</td>
<td>21</td>
<td>3-5</td>
<td>Early signs and symptoms</td>
<td>Progress to moderate paralysis</td>
</tr>
<tr>
<td></td>
<td>33138</td>
<td>F.</td>
<td>25</td>
<td>2-5</td>
<td>Extensive paralysis</td>
<td>No progression</td>
</tr>
<tr>
<td></td>
<td>35182</td>
<td>M.</td>
<td>30</td>
<td>2</td>
<td>Early signs and symptoms, inconaguable blood</td>
<td>No progression</td>
</tr>
<tr>
<td></td>
<td>29168</td>
<td>M.</td>
<td>10</td>
<td>24</td>
<td>Extensive paralysis</td>
<td>Progress to probable death</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(21 at out-station)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>31019</td>
<td>M.</td>
<td>28</td>
<td>2</td>
<td>Doubtful early signs</td>
<td>No progression</td>
</tr>
<tr>
<td></td>
<td>31524</td>
<td>F.</td>
<td>11</td>
<td>0-5</td>
<td>Severe early signs and symptoms, inconaguable blood</td>
<td>Died</td>
</tr>
<tr>
<td></td>
<td>32792</td>
<td>F.</td>
<td>25</td>
<td>4</td>
<td>Early signs and symptoms</td>
<td>Progress to slight paralysis</td>
</tr>
<tr>
<td></td>
<td>34774</td>
<td>M.</td>
<td>6</td>
<td>2</td>
<td>Early signs and symptoms, inconaguable blood</td>
<td>No progression</td>
</tr>
</tbody>
</table>

*No change: no progression expected and none occurred.
*Signs and symptoms: headache and/or vomiting, pain in the groin, abdominal pain, swelling or vomiting blood, tender regional lymph glands.

The image contains a table summarizing the clinical details and response to antivenene therapy in 28 cases of snakebite. The table categorizes patients by type of bite, provides the hospital number, sex, approximate age, hours between bite and antivenene administration, the condition when antivenene was given, and the progress after antivenene administration.

**Reactions to Antivenene**

Eleven of the 28 patients had some form of reaction to the antivenene. Eight developed urticaria or an itchy skin within eight minutes or more of commencing the injection, and sometimes not until the end of the injection.

Five had a shivering attack or rigor, often followed by a rise of temperature as high as 105.6°F. This reaction usually occurred within the hour after the antivenene was injected. Two patients complained that their abdominal pain was aggravated by the antivenene during the injection. One patient complained of severe pain in the arm along the course of the brachial vein as the antivenene was injected, the pain ceasing when the injection was stopped and started again when the injection was recommenced. One patient developed an increase in oral secretions and wanted to vomit; one became restless; one developed a loose cough and a wheeze; one patient developed anaphylactic shock.

No patient died as a consequence of the antivenene administration.

**Discussion**

Death adder and Papua-New Guinea polyvalent antivenenes are highly effective antivenenes in the treatment of death adder envenomation and therefore also in the prevention of death adder snake-poisoning. It is claimed that it is never too late to inject cobra antivenene (Strover, 1953), and that even when a patient is moribund, recovery may still occur (Ahuja and Singh, 1954), but Mackie (1933) indicated that normally the patient had to have the antivenene "within a reasonable time of the bite for it to be effective", and Acton and Knowles (1915) stipulated administration before two-thirds of the anticipated time before death had elapsed. Death adder venom resembles cobra venom more closely than any other Australian venom, both in its toxic constituents and in its response to antivenene, and it is hoped that further clinical experience will indicate that it is never too late to inject death adder antivenene.
Unfortunately, this hope does not seem to hold for taipan and Pampus black snake antivenenes. After taipan and Pampus black snake bites a stage seems to be reached when the antivenene ceases to be of value in preventing death, for they do not halt the progress of the patient or prevent death to a fatal issue. They may at this late stage possibly still act beneficially on the coagulation defect and the hemorrholsy if present. Eleven is particularly disappointing to find that, in cases 26580, 31524 and 37439, even when the antivenene was given within one hour, half an hour and five hours of the bite, and in doses of two, three and four times the recommended dose, the antivenene did not in one case and would not in the other two cases have prevented a fatal outcome. These three patients were all children and must have received large doses of venom relative to their size.

Even though the antivenene may not have prevented a fatal outcome in these patients and others in whom the paralisys continued to progress, it is still possible that the antivenene may yet serve some useful purpose in treatment. For apart from its beneficial effect on the blood, if the antivenene can prevent complete diaphragmatic paralysy and thus eliminate the need for artificial ventilation of the patient for periods of up to one week or more, it has performed a useful function. It is impossible to know whether the absence of serious paralysy of the diaphragm in some cases is due to the antivenene administered or to the smaller dose of venom injected. In some cases it would appear probable that the antivenene has limited the extent of the paralysis.

It is possible that more massive doses of antivenene may further limit or even reverse the paralysy produced by the venom of the taipan and Pampus black snake, for up to 600 ml. of cobra antivenene may be required to reverse the paralysy produced by cobra venom (C. Puranandam, 1967, personal communication). If this was to happen, evidence of slight improvement in the paralysy of at least one of the many cases of taipan and Pampus black snake bites now treated with smaller doses of these antivenenes should have occurred. The clinical response to antivenene of patients envenomed by the taipan and the Pampus black snakes differs from that of those injected with death adder venom. This may be due to relatively less potent taipan and Pampus black snake antivenenes or, more probably, to a basic difference in the response of the Australian thrombase-containing elapine venoms to antivenene (Campbell, 1966).

Furthermore, in experiments on animals injected with tiger snake venom (a thrombase-containing venom) Kellaway (1932) was unable to demonstrate any dramatic reversal of the paralysis with doses of antivenene compared with the times the in-vitro neutralizing dose. However, the antivenene was injected 24 hours after the venom. On the contrary, J. J. Graydon (personal communication, 1966) states that, in experiments conducted at the Commonwealth Serum Laboratories over 20 years ago on moribund rats poisoned by tiger snake venom and copperhead venom (which does not contain thrombase), the paralysy was reversed with tiger snake antivenene.

The fibrinogenopenia produced by the thrombase in the venom is not usually of clinical importance unless some wound is present which then continues to bleed. This bleeding does complicate the management of a tracheotomy. In the Australian literature there is one case of fatal cerebral hemorrhage attributed to snake bite (Foxton, 1914). The occurrence of black tarry stools 48 hours after a serious snake bite has also been reported (Mueller, 1903), and serious hemorrhages are not uncommon, so that there are potential hazards from the fibrinogenopenia other than bleeding wounds. After the antivenene, the clotting defect starts to improve within five hours, and the blood clots normally within 48 hours of injecting the antivenene. It is not known if this is an accelerated rate of recovery compared to the natural recovery rate after the injection of venom, but it probably is.

When antivenene is given, the hemoglobinuria ceases within four to eight hours. Again, the natural course of this toxic effect of the venom has not been observed.

the absence of antivenene administration, but the antivenene is probably of value in neutralizing the hemolysin in the venom.

In a previous paper (Campbell, 1964), it was reported that 21 out of 35 patients receiving intravenous injections of antivenene for snake bite had some form of immediate reaction to the serum. Eleven particularly disappointing to find that, in cases 26580, 31524 and 37439, even when the antivenene was given within one hour, half an hour and five hours of the bite, and in doses of two, three and four times the recommended dose, the antivenene did not in one case and would not in the other two cases have prevented a fatal outcome. These three patients were all children and must have received large doses of venom relative to their size.

Even though the antivenene may not have prevented a fatal outcome in these patients and others in whom the paralysy continued to progress, it is still possible that the antivenene may yet serve some useful purpose in treatment. For apart from its beneficial effect on the blood, if the antivenene can prevent complete diaphragmatic paralysy and thus eliminate the need for artificial ventilation of the patient for periods of up to one week or more, it has performed a useful function. It is impossible to know whether the absence of serious paralysy of the diaphragm in some cases is due to the antivenene administered or to the smaller dose of venom injected. In some cases it would appear probable that the antivenene has limited the extent of the paralysy.

It is possible that more massive doses of antivenene may further limit or even reverse the paralysy produced by the venom of the taipan and Pampus black snake, for up to 600 ml. of cobra antivenene may be required to reverse the paralysy produced by cobra venom (C. Puranandam, 1967, personal communication). If this was to happen, evidence of slight improvement in the paralysy of at least one of the many cases of taipan and Pampus black snake bites now treated with smaller doses of these antivenenes should have occurred. The clinical response to antivenene of patients envenomed by the taipan and the Pampus black snakes differs from that of those injected with death adder venom. This may be due to relatively less potent taipan and Pampus black snake antivenenes or, more probably, to a basic difference in the response of the Australian thrombase-containing elapine venoms to antivenene (Campbell, 1966).

Furthermore, in experiments on animals injected with tiger snake venom (a thrombase-containing venom) Kellaway (1932) was unable to demonstrate any dramatic reversal of the paralysy with doses of antivenene compared with the times the in-vitro neutralizing dose. However, the antivenene was injected 24 hours after the venom. On the contrary, J. J. Graydon (personal communication, 1966) states that, in experiments conducted at the Commonwealth Serum Laboratories over 20 years ago on moribund rats poisoned by tiger snake venom and copperhead venom (which does not contain thrombase), the paralysy was reversed with tiger snake antivenene.

The fibrinogenopenia produced by the thrombase in the venom is not usually of clinical importance unless some wound is present which then continues to bleed. This bleeding does complicate the management of a tracheotomy. In the Australian literature there is one case of fatal cerebral hemorrhage attributed to snake bite (Foxton, 1914). The occurrence of black tarry stools 48 hours after a serious snake bite has also been reported (Mueller, 1903), and serious hemorrhages are not uncommon, so that there are potential hazards from the fibrinogenopenia other than bleeding wounds. After the antivenene, the clotting defect starts to improve within five hours, and the blood clots normally within 48 hours of injecting the antivenene. It is not known if this is an accelerated rate of recovery compared to the natural recovery rate after the injection of venom, but it probably is.

When antivenene is given, the hemoglobinuria ceases within four to eight hours. Again, the natural course of this toxic effect of the venom has not been observed.

SUMMARY

1. Twenty-eight patients with established snake envenemation were treated with antivenene at the Port Moresby General Hospital over a period of 21 months. The results of the antivenene therapy and side reactions to it are summarized.

2. Severe paralysy produced by death adder venom was rapidly reversed with antivenene. In its response to antivenene, death adder venom appears to differ from taipan and Pampus black snake venoms.

3. If injected within a few hours of the bite of a taipan or Pampus black snake, antivenene is considered in most cases to prevent the development of, or limit the extent of, the muscle paralysy produced by the neurotoxins of the venoms, and to counteract the effects of the hemolysin and thrombase in the venoms.

4. When injected some time after the bite of a taipan or Pampus black snake venom, antivenene, in doses up to four
times the recommended dose, would not have prevented death but, in some cases, may have limited the extent of the muscle paralysis which developed.

5. Approximately 25% of patients receiving antivenene had some reaction to it, and 3% developed potentially fatal anaphylactic shock.

6. It is recommended that in the case of bites from Australian snakes with thrombosis in their venom (taipan, tiger, brown, common black and Papuan black snakes), if paralysis is present, at least 10 times the recommended dose of specific antivenene should be injected intravenously, in the hope that the paralysis may be reversed by the antivenene.

ACKNOWLEDGEMENTS

I wish to thank Dr. J. J. Craydon of the Commonwealth Serum Laboratories, Melbourne, and Professor R. H. Black of the School of Public Health and Tropical Medicine, Sydney, for their helpful comments on the article. The paper is published with the approval of Dr. R. F. R. Scragg, Director of Health, Territory of Papua and New Guinea.

REFERENCES


ARTHUR, M. (1919), "Le venin de cobia est un curare", Arch. sous-marines, 1: 3.


Apple, potato, spinach, tomato. All are plants used in the daily cuisine of many nations. All contain deadly poisons. None of these plants readily comes to mind as a potential killer. The fact is that most laymen, asked to cite examples of poisonous flora, would name the plants whose sinister reputation has come through folklore of fear or true danger. Anyone who has even a nodding acquaintance with Greek history recalls that Socrates met his death through the offices of a potion of hemlock. From Shakespeare to Charles Addams, scores of ill-fated characters have been dispatched by a nip of nightshade, a dose of dogbane, a touch of toadstool...

While the formidable effects of poisonous plants cannot be overstated, instances of poisoning to humans usually result from isolated accidents, such as children being attracted to interesting looking shoots, mushrooms, or flowers. Although many fruits and vegetables found at the supermarket or in the garden contain poisons that could cause serious injury or death, there are two inherent protective controls: poison in foods is found in parts of the plant we do not usually eat. When the poison exists in the edible portion, abnormal quantities must be consumed before the toxic effects are felt. Thus, while potato plants contain solanine, which is extremely toxic, it is concentrated in the berries, not the tubers that we eat. Tomato vines also contain solanine. Spinach could conceivably block the absorption of nutrients, and we could certainly find our way to a fatal diet...