the known administration of arsenic (32 gr.—2.079 g.) ; second, symptoms known to be caused by arsenic were observed before death ; and, finally, enough arsenic was found in the liver to account for death. In this connexion it is important to differentiate between examples of arsenical encephalitis following acetarsol administration and acute arsenical poisoning as described here. Although clinically there may be few distinguishing features, post-mortem findings, and in particular toxicological analysis, will readily provide the answer. Encephalitis may result from very small amounts of organic arsenical—for example, intravenous arsphenamine—but acute poisoning must be related to the amount ingested and may have medico-legal significance.

Summary and Conclusions

A fatal case of acute arsenical poisoning due to acetarsol vaginal pessaries is reported.

The treatment of vaginitis due to infection with *Trichomonas vaginalis* is often satisfactorily and safely carried out with acetarsol (stovarsol or S.V.C.) pessaries. Nevertheless, there is a very small risk of a mild skin reaction, and if treatment is continued the reaction may be severe and generalized. Such reactions may occur in the course of prolonged treatment or they may arise when treatment is recommended after a previous sensitizing dose. Jaundice or haemorrhagic encephalitis may also occur as a sensitivity response to organic arsenicals.

There is evidence that arsenic was absorbed from the vagina in the present case, and in theory either acute arsenical poisoning or haemorrhagic encephalitis could have followed. The distinction is important because the mechanism of production is quite different. Arsenical encephalopathy is not necessarily related to the amount of arsenic present, while acute arsenical poisoning is directly dependent on the amount of the drug that is absorbed. In fact, no such encephalitis was found, and there was enough arsenic in the liver to show that death was due to direct arsenical poisoning. This occurred as the result of packing the vagina on two out of three days with a total of 30 acetarsol pessaries. Such intensive treatment is sometimes recommended for resistant cases, but the presence of a vaginitis almost certainly increases the absorption, and in our opinion the method should be abandoned.

Our thanks are due to Dr. Dudley Hart, who took over the medical treatment of the patient when she was transferred, and to Dr. G. Thurston, H.M. Coroner for West London, for the post-mortem report.

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MYOGLOBINURIA AND SEA-SNAKE-BITE POISONING*

BY

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The clinical paradox of trismus yet paresis elsewhere originally stimulated investigations of sea-snake-bite poisoning (Reid, 1956a). Experimentally, sea-snake venom is feebly haemolytic: theoretically, a dose of venom sufficient to cause haemolysis should inevitably be fatal. Yet patients survived despite apparent haemoglobinuria. In these survivors, moreover, there was no evidence of excessive haemolysis. These anomalies were resolved in 1957 when it was realized that the urinary pigment was myoglobin, not haemoglobin. The purpose of this paper is to present case records and clinical investigations of patients selected as elucidating the pathogenesis of sea-snake-bite toxæmia.

Material

During 1957–9 38 patients with sea-snake-bite were personally observed in hospitals. The sea-snake was reliably recognized in 25 cases (23 were in fishing folk) ; in four subjects—all bathers—typical toxæmia followed ; and the remaining nine patients (“probable cases”) were bitten in the sea, felt no local pain after the incident (thereby excluding fish-stings), and had bite-marks compatible with those of a sea-snake. In this selected series of 38 victims serious poisoning followed in only nine cases (five fatal, three severe, one moderate). Trivial toxæmia resulted in two instances and no poisoning followed 27 bites (18 unequivocal, 9 “probable” as defined above). The following case records and investigations are representative of the minority developing poisoning.

Case 1

An Englishman aged 32 was bitten in the left calf while bathing at 4 p.m. on September 2, 1957. The first symptom was slight giddiness at 4.25 p.m. On reaching hospital at 4.30 p.m. the back of his neck felt stiff and ached, particularly on moving his head. At 4.35 his tongue felt stiff and was slightly swollen, there was some pain on swallowing, and all four limbs were stiff on moving “as if I had taken a lot of exercise.” At this time the admission doctor found the B.P. 140/92. Dr. C. P. Cheah, who had examined the patient for life insurance on September 8, 1955, kindly informed me subsequently that the B.P. was then 125/68. At 6.30 p.m. the B.P. was 120/100, and on the left calf were multiple pin-point marks which could only have been made by at least two bites.

His pupils were equal, not unduly dilated, and reacted briskly to light. Abdominal reflexes were present, plantar responses flexor. He was unable to look to the left, otherwise eye movement was normal. He could clench his jaws strongly and open them 35 mm. (between teeth edges). Showing his teeth or grinning was difficult owing to stiffness of his face, but there was no asymmetry of movement. Palate movement and coughing appeared normal, but the latter caused pain in the abdomen and lower ribs. Swallowing of fluids was painful although not otherwise difficult. Hearing a watch and appreciation of light touch, pinprick, joint movement, and vibration were normal. There was no nystagmus. He could lift his head off the bed against strong pressure, but turning it to either side was painful. He could

*Based partly on a thesis for the degree of M.D. in the University of Edinburgh.

sit up spontaneously (although this made him giddy) and could lift all four limbs off the bed. They were tender on pressure but not swollen or unduly hard. Active or passive flexion was extremely painful—much more so than pressure. He described this pain as "cramping" and groaned with the severity. Muscle tone was difficult to judge in the circumstances but was probably normal. Tendon reflexes were brisk.

At 7.30 p.m. he was unable to move his eyes in either lateral direction. Vertical movement was about 50% normal. Jaw-opening was 33 mm. At 9.30 p.m. he felt "lousy." Both pupils were dilated but reacted to light. They did not constrict when he attempted to accommodate—he was unable to turn his eyes inwards for this and saw double when my finger was brought within 2 ft. (60 cm.) or less. Visual acuity (reading newsprint) was normal.

FIG. 1.—Electrocardiograms showing progressive hyperkalaemia.

Maximal jaw-opening was now 23 mm. He could not protrude his tongue beyond the teeth or lift his head off the bed, and could raise the heels and right arm off for only a few seconds. The left arm was splinted for the intravenous drip of 20% glucose (1 litre was given rapidly between 7.30 and 9 p.m.). At 10 p.m. his pupils were equally dilated, but the right one no longer reacted to light. The left reacted slowly. Ptosis was now evident. He tried to swallow water but had great difficulty with it. Passive movement of limbs continued to be very painful.

At 11 p.m. the nurse attempted to pass a Ryle tube and he vomited. I immediately turned him in to the prone position and then lifted the end of the bed on to high blocks. No vomit was inhaled. Coughing was feeble but respiration appeared satisfactory. At 11.15 p.m. the first electrocardiogram (E.C.G.) was taken (see Fig. 1). Increased sweating was noted, B.P. was 160/120, breathing had become shallow, and breath sounds were faint. At 11.45 p.m. he was comatose, fingers cyanosed, B.P. 180/125. It was therefore decided to do a tracheostomy and give intermittent positive-pressure artificial respiration (I.P.P.R.) with an Oxford Radcliffe machine. The anaesthetist, Dr. L. T. Scott, was surprised how strongly he had to hold the patient's arm to give the atropine and thiopentone injections. When I.P.P.R. was started it was soon apparent that he was "fighting the machine." We were naturally reluctant to give D-tubocurarine in view of sea-snake venom itself having a neuromuscular blocking action in animals, but his condition was desperate, and therefore at 1 a.m. on September 3 30 mg. of D-tubocurarine was injected intravenously. Cyanosis rapidly disappeared.

For the next two hours a good colour and breath sounds with minute-volume 10.5–11.5 litres continued, yet the B.P. remained 150–170/120–130. At times both legs were moving slightly and his arms had to be held down. At 3.40 a.m. he became cyanosed, no pulse was felt, and the B.P. could not be recorded. The second E.C.G., at 3.45 a.m., showed hyperkalaemic T waves and widening of the angle between S and ST segment (see Fig. 1). An intravenous drip of noradrenaline was started at 4 a.m., but there was no improvement. At 5.05 a.m. the heart could no longer be heard and no E.C.G. record could be obtained—13 hours after the bite.

Case 2

At 5.15 p.m. on June 13, 1958, a 10-year-old Indian schoolboy was having a swimming race when his right foot touched the mud and he felt a prick. He thought it was a nail and reached down to remove it, but instead felt a sea-snake. He returned to school and started a game of marbles, which entailed frequent bending. At 5.45 p.m. he noticed increasing pains in both buttocks. At 5.55—on his way to hospital—the pains spread to his throat, neck, and hips. He walked 100 metres from the car to the admission office, and on arriving at 6 p.m. said he could not move his limbs. The back was also painful and any movement made the pains much worse. His mouth felt stiff.

On examination two fang marks 15 mm. apart were seen on the right instep. He was not sweating unduly; the B.P. was 110/85. He lay on his back with forearms and wrists flexed, legs straight. Power and tone were difficult to estimate because of the distress any active or passive movement produced. He could lift his head and limbs off the bed but was unable (or unwilling) to sit up. Passive movement, however, appeared to be resisted by powerful contraction in the opposer muscle groups. Progress thereafter is summarized in Fig. 2. The blood-pressure remained normal until 15 minutes before death. Respiratory failure was counteracted by I.P.N.P.R. (positive-negative pressure) and hyperkalaemia by rapid infusion of glucose and calcium, yet the patient died 14½ hours after the bite.

Case 3

A Chinese mechanic aged 17 was bitten on the left lower leg at 5.45 p.m. on May 14, 1957, while bathing. Frontal headache started at 6.30; pains in the throat, right shoulder,

and chest, with thirst and increased sweating, at 6.45. At hospital, at 7 p.m., he had difficulty in raising his limbs from the stretcher; sweating was profuse, and B.P. 140/90. At 9.15 p.m. he was unable to sit up without help but could lift his head against resistance. Limb power was objectively

Fig. 2.—Clinical course to death (Case 2). Paresis follows in the wake of muscle-movement pain. Death occurred despite adequate artificial respiration and prevention of hyperkalaemia.

I.P.N.P.R. = Intermittent positive/negative-pressure artificial respiration.

Paresis.—5=respiratory failure; 4=unable to lift one or more limbs; 3=unable to lift head; 2=unable to sit up spontaneously; 1=objective weakness less than 2.

Areflexia.—5=7–8 tendon reflexes absent; 4=5–6 absent; 3=3–4 absent; 2=1–2 absent; 1=present but weak.

Myoglobinuria.—3=dark brown, red, or black, spectroscopically positive; 2=light brown or dark yellow, spectroscopically positive; 1=benzidine-positive, spectroscopically negative.

Fig. 3.—Clinical course to recovery (Case 3). Muscle-movement pains recede before paresis. Tendon reflexes recover quickly. Raised blood urea with low urinary urea reflects renal damage. (Notation as in Fig. 2.)

normal despite his claim that he "could not move." All limbs were held flexed, and passive movement was disliked owing to the pain it caused. Muscles were tender on pressure, but this did not cause as much distress as passive movement. Tendon reflexes were present. Movement of eyes, face, tongue (which was moist), palate, and shoulders was full. On the lower left leg fang marks 8.5 mm. apart could be easily distinguished from two maxillary and four pterygoid teeth marks. The remaining findings were not abnormal.

Further progress is illustrated in Fig. 3. At 9 a.m. on May 15 muscle pains and tenderness were more severe in the neck, shoulders, and thighs; thirst continued. At 5 p.m. there was objective weakness of arm abduction but no other change in muscle power. Arm-jerks were absent, knee- and ankle-jerks present. On May 16 muscle pains were worse. Objectively, muscle power was now significantly diminished in the neck, back, and proximal limbs. Neostigmine 2 mg. was injected intravenously, but no benefit was observed. On May 17 the shoulder, arm, and thigh muscles were weaker. On May 18 pains and tenderness started to recede but paresis had increased. Both scapulae showed "winging," pectorals were weak, and hand-grip was feeble. Knee-jerks were now absent and ankle-jerks very sluggish.

During the second week paresis in proximal limbs, trunk, and neck remained essentially the same, but further loss of power occurred in forearm and hand muscles. By the middle of the second week tendon reflexes were all brisk except the ankle-jerks. The urine still contained myoglobin but the colour was lighter. From the start of the third week there was a progressive improvement in power and a recession of trismus and myoglobinuria (see Fig. 3). He was able to lift his head off the bed and could sit up by rolling on to his right side and helping himself up with his right arm like a patient with muscular dystrophy. By the sixth week lower-limb power appeared objectively normal. Arm abduction, forearm extension, and hand flexion were weaker on the left than on the right side. He could sit up spontaneously 10 weeks after the bite. By mid-September press-ups had become normal compared with a control patient of his own age and build; hand-grip was still weaker on the left than on the right. In November he had fully recovered.

In the first week after the bite the B.P. was 120/70-80, but during the next 10 days, when there was non-oliguric renal insufficiency (see Fig. 3), mild hypertension (140-145/90-100) was present. Thereafter the B.P. returned to normal. There was no clinical or radiological evidence of any cardiac or lung lesions, but there were E.C.G. changes. Dominant R waves developed in right chest leads, and T waves rose from 4 mm. in height 15 hours after the bite to 14 mm. three weeks later, although serum potassium on the 22nd day—the only estimation made—was 4.6 mEq/l. Blood urea at this stage was already falling.

Case 4

An Indian boy aged 15 was wading ashore from his boat at 9 a.m. on May 20, 1958, when he was bitten on the inside of his right ankle. When he reached the hospital at 10.30 a.m. he felt pains in the right leg, elbow, and neck. Physical examination was negative. He was advised to drink as much fluid as he could manage. The third urine specimen (six hours after the bite) was positive for occult blood and the next two (9 and 11 hours after) were strongly positive. The sixth (17 hours after) was still positive but subsequent specimens were negative. The limb and neck pains continued until May 21.

Investigations

Haematology.—Leucocytosis was present in all the subjects in whom poisoning was serious, counts exceeding 20,000 being confined to fatal cases; the degree and duration correlated approximately with the severity of the toxæmia. Eosinophils were not

increased. No evidence of abnormal haemolysis or coagulation defect was found. Reticulocytes, platelets, saline fragility, serum bilirubin, urinary urobilinogen, bleeding-time, coagulation time, one-stage prothrombin time, direct Coombs, Schumm's, Donath-Landsteiner, and Kahn tests were always normal. The erythrocyte sedimentation rate was raised in Case 3 and normal in another severe case.

Biochemistry.—In each of the nine serious cases myoglobinuria was identified by comparison spectroscopy, the difference from a control urine with haemoglobin being unequivocal. The earliest visible change in the urine was a dusky yellow colour, when protein tests and the benzidine or occult blood test would be positive but spectroscopy negative. Urine of this nature was passed six hours after the bite in Case 1, eight hours after in Case 4. Within an hour or less the urine became brown or red and was then spectroscopically positive—in Case 2 this type of urine was passed three hours after the bite. Seven victims did not pass urine until 7-22 hours after the bite, when the colour was already dark brown or red. The patient who survived the most severe poisoning (Case 3) excreted roughly 18 g. of myoglobin during the first 17 days after his bite, thus losing about one-tenth of his total myoglobin. In another severe case the subject lost about 16 g. in a week. An important pathogenic observation in the two trivial cases was the occurrence of myoglobinuria even though poisoning was so minimal that paresis could not be detected. The urine reaction might be acid or alkaline. Microscopy showed granular casts if pigment or protein was present, but significant red blood cells were absent. Although oliguria was not a feature in Case 3, the findings suggested renal damage (see Fig. 1). Follow-up studies indicated that this might be permanent in some cases.

Progressive hyperkalaemia occurred in Cases 1, 5, and 6 (see Fig. 1). Plasma potassium and blood creatine and creatinine remained normal in Case 2 up to three and a half hours before death. In Case 5 blood creatine rose from 0.4 (14½ hours after the bite) to 2.7 mg./100 ml. at death (18½ hours after the bite). Creatinine remained normal. Urine creatine totalled 59 mg., creatinine 250 mg., in 318 ml., obtained four hours before and at death (not estimated in Case 2). Plasma sodium and blood urea remained within normal limits in Cases 2, 5, and 6, but in Case 1 blood urea rose from 37 mg./100 ml. seven hours after the bite to 70 mg. at death.

Plasma protein electrophoresis suggested liver damage in one severe case (not done in others), but at follow-up studies of patients with severe or moderate poisoning liver function as judged by bromsulphalein clearance test was normal. Lumbar puncture in a case previously recorded (Reid, 1956b) revealed normal cerebrospinal fluid.

Electrocardiography.—Serial records with standard, unipolar, and eight chest leads (V_4R-V_6) were taken throughout toxæmia from 9 of the 11 patients. In Case 2 (up to two hours before death), the single moderate case, and one of the two trivial cases, records remained normal. In Cases 1, 5, and 6 signs of progressively severe hyperkalaemia developed (see Fig. 1). In Case 5 and all three patients with severe poisoning, monophasic or dominant R waves were present in V_4R . In Case 3 and one of the other severe cases R was also dominant in V_3R and V_1 . In follow-up

studies the pattern of right ventricular dominance persisted unchanged in the latter case. However, this 11-year-old boy was an asthmatic and therefore the significance of the E.C.G. records in relation to sea-snake poisoning is uncertain. In Case 3 there was some regression of the pattern after his discharge. One year after the bite R equalled S in V_1 and V_3R , and 16 months afterwards S exceeded R in V_4R-V_1 . But ventricular activation time in V_1 remained prolonged at 0.05 second.

Electrodiagnosis.—In the three severe cases there was no qualitative change in serial tests with faradic and galvanic stimulation. Contraction in response to faradic current remained brisk although diminished in amplitude—there was no reaction of degeneration. Recovery of normal amplitude was rapid (two to three weeks). Apparatus for intensity-duration curves and electromyography was not available.

Neostigmine Test.—Because experimental work in animals suggested that sea-snake venom acts by blocking the neuromuscular junction, neostigmine was given intravenously in a case already reported (Reid, 1956b) and in the three severe cases, but no improvement was observed.

Muscle Biopsy.—In Case 3 biopsy of the left deltoid muscle on the third day after the bite, when muscle-movement pains were maximum, showed necrosis of 30% of the fibres. Right deltoid biopsy six months later showed fine scarring (Marsden and Reid, 1961).

Radiology.—Chest radiographs were taken in all except fatal cases at varying times after the bite during the toxæmia and at follow-up studies. No abnormality of the heart shadow or lung fields was observed except for increased markings in the asthmatic victim. Dr. J. F. Goodwin kindly confirmed the absence of radiological changes suggesting pulmonary hypertension (Goodwin, 1958). Intravenous pyelograms were normal in Case 3 and the asthmatic patient.

Discussion

Experimentally, Barnes and Trueta (1941) found that cobra venom, because of its low molecular weight (under 5,000), was rapidly absorbed through the capillaries direct into the blood-stream. In contrast, venoms with higher molecular weights were absorbed more slowly via the lymphatics. In human victims of poisoning from sea-snake-bite the latent period of 30–60 minutes has been remarkably constant irrespective of the site of the bite or of the venom dose as judged by subsequent progress. J. E. Carey (personal communication, 1959) considered the molecular weight of *E. schistosa* venom to be 9,000 or under. These findings suggest that absorption of sea-snake venom in human victims is a process of diffusing up the interstitial tissues either into capillaries direct or via lymphatics and thoracic duct, through the pulmonary circuit, and thence into the systemic circulation. From here the venom affects skeletal muscles according to blood flow and anatomical propinquity to the pump. Thus it is that throat, neck, back, or proximal limb muscles are the first to show the characteristic stiffness and muscle-movement pains.

Hitherto it has been assumed from animal experiments that sea-snake venom is predominantly neurotoxic to human victims. At necropsy on human patients, no histological abnormalities have been found in the nervous system—but this is also the case in tetanus

toxæmia, and the primary site of action of tetanus toxin on nervous tissue is not disputed. Clinically in human patients with sea-snake poisoning the outstanding early feature is muscle-movement pain. However, such pains are also common in myalgic encephalomyelitis and the preparalytic phase of poliomyelitis. It might be argued that the muscle-movement pains are merely early signs of neurological involvement. Undoubtedly paresis and areflexia eventually ensue. Might the myoglobinuria not be secondary to a neuropathic paresis? Personally I am convinced that in human subjects sea-snake venom acts primarily on skeletal-muscle cells for the following clinical reasons:

1. Muscle-movement pains precede paresis by several hours in rapidly fatal cases or by as long as 24 hours in severe poisoning.

2. Much of the paresis is apparent rather than real, as shown by objectively normal limb power in Case 3 when the patient said he "could not move," also by various activities late in the paresis of fatal cases.

3. Trismus in tetanus is neurogenic, but it differs strikingly from trismus in sea-snake toxæmia. The latter can be reduced by sustained pressure on the lower jaw—this does not increase the gape in tetanus at all. Secondly, the jaw-jerk is very brisk in tetanus, and absent or sluggish in sea-snake poisoning. This suggests that the trismus and stiffness in limbs and trunk are due to the splinting reaction of intact muscle cells protecting injured cells against further damage by stretching.

4. No fibrillation or muscle fasciculation is seen at any stage.

5. In severe cases there is no qualitative change in response to faradic and galvanic stimulation—this is typical of a myopathic lesion (Walton and Adams, 1958).

6. Myoglobinuria may be apparent before paresis, and is present in minimal poisoning with no detectable paresis.

7. There is no evidence of sensory, cerebellar, or meningeal involvement and, except in terminal toxæmia, no mental or higher cerebral upset.

8. Necropsies show widespread myonecrosis even when victims die only 13 or 14½ hours after the bite (Marsden and Reid, 1961).

The flaccid paresis which follows later can be explained by progressively increasing muscle damage. Absent tendon reflexes have been recorded in purely myopathic conditions such as polymyositis (Walton and Adams, 1958) and do not necessarily indicate a neural lesion. If, however, the loss of tendon reflexes and their rapid return in some cases do reflect a neurotoxic as well as myotoxin action, the absence of sensory change, fasciculation, and wasting suggest a block at the myoneural junction. This would be due to failure of the end-plate to respond to the transmitter (Lilienthal and Zierler, 1957) rather than to a curariform type of block, since neostigmine is quite ineffective.

There is no pain in the joints and, unlike the muscles, they are not tender. Minimal joint movement not entailing significant change in muscle length is painless: once myalgia has resolved, full joint movement is painless. These facts and the myoglobinuria exclude a primary joint lesion.

In contrast to extensive skeletal myonecrosis, no histological abnormality is found in smooth muscle or the myocardium. However, the E.C.G. pattern of right ventricular dominance suggests some change in the myocardium or pulmonary vessels. There is no clinical, radiological, or histological evidence of pulmonary vasoconstriction, and systemic hypertension in the absence of respiratory failure is exceptional.

Gailani, Danowski, and Fisher (1958) found similar E.C.G. changes in patients with muscular dystrophy, and they excluded pulmonary hypertension or right heart enlargement by cardiac catheterization. They attributed the changes to conduction defect in the myocardium. This may be the explanation of the abnormal E.C.G.s in sea-snake poisoning. Yet it is peculiar that a toxæmic conduction defect should persist as long as one and a half years after the bite. In Case 1 there was persistent systemic hypertension (known to have been absent prior to the bite) right from the start of the toxæmia. Early hypertension was not present in the other patients, so a direct venom effect on smooth muscle of arterioles seems unlikely. Could it have been a renal pressor factor secondary to kidney damage by the venom? There has been histological evidence of kidney damage in most patients coming to necropsy. Clinically, shock is not a feature—hypotension was not observed except within an hour or two of death.

Although serum bilirubin remained normal, electrophoresis of plasma proteins suggested liver dysfunction. Kidneys showed tubular necrosis in three necropsies (Marsden and Reid, 1961), and in Case 3 the raised blood urea with low urinary urea and "fixed" specific gravity indicated serious renal damage although the urine volume was normal. The constant thirst, with a moist tongue, is attributed to cellular dehydration or increased osmolarity of extracellular fluid, although it may be due to a direct biochemical effect on the thirst centre (Fourman and Leeson, 1959). As the venom disrupts muscle cells to the extent of releasing myoglobin there must be a concomitant escape of potassium, magnesium, and other substances into the interstitial tissues. Hyperkalaemia was a major factor in three deaths. Potassium and magnesium upset at the end-plate might be further components in the late-developing paresis.

Myoglobinuria is easily overlooked or mistaken for haemoglobinuria. It is a sign of skeletal-muscle damage, probably involving myonecrosis, which may be caused by a variety of insults, including: (1) Trauma, which may be physical, such as crush injuries (Minami, 1923; Bywaters and Beall, 1941), severe assault (de Langen, 1946), or status epilepticus (Iversen, 1948); electrical (Fischer and Rossier, 1947); or by burns (Campbell and Ezrin, 1954). (2) Inflammatory, due to bacterial infections, such as typhoid and gas-gangrene, leptospiral (Adams, Denny-Brown, and Pearson, 1953) and viral infections (Lépine, Desse, Sautter, 1952), and polymyositis (Günthür, 1924; Paul, 1924; Walton and Adams, 1958). (3) Endocrine, such as myxoedema (Marshall and McCaughey, 1956). (4) Ischaemic (Bywaters and Stead, 1945; Elek and Anderson, 1953). (5) Familial (Louw and Nielsen, 1944; Hed, 1955). (6) Toxic causes, which include Haff disease (Hed, 1955), alcohol and barbiturates (Fahlgren, Hed, and Lundmark, 1957), carbon monoxide (Loughridge, Leader, and Bowen, 1958), and, now, sea-snake poisoning. (7) Idiopathic myoglobinuria with or without dystrophy (Pearson, Beck, and Blahd, 1957).

The similarities of sea-snake poisoning to Haff disease are striking—muscle-movement pain and a feeling of stiffness, sweating, thirst, leucocytosis, and a proneness to acute renal failure. The name comes from the sea inlet Frisches Haff, where epidemics occurred in 1924–5, 1932–3, and 1940. Berlin (1948) observed a small outbreak in 1942–3 around Lake Yusen just south of

Mariestad, in Sweden. The great majority of victims were fishermen (but sea-snakes cannot be incriminated as they have never been recorded from these regions). The cause was never elucidated, although Berlin thought it might be an aneurine-inactivating factor similar to that producing Chastek paralysis in foxes. Because of this theory, two patients with severe sea-snake poisoning were given parenteral vitamins, but no convincing improvement resulted.

To summarize pathogenesis so far as clinical features assist elucidation, the tissue primarily attacked by sea-snake venom in human victims is skeletal muscle. The attack is generalized throughout the body, but certain areas such as the neck, trunk, and proximal limbs bear the brunt. There is electrocardiographic evidence that the myocardium may be affected. Kidneys and liver are usually involved and nerve tissues may possibly be implicated later, but it is uncertain whether these are direct effects of the venom, due to secondary toxic metabolites, or caused by a combination of these factors.

Summary

Clinical observation indicates that sea-snake venom is primarily myotoxic to human victims. Generalized muscle-movement pains and myoglobinuria are the outstanding symptoms of poisoning. There is a close similarity to other syndromes with myoglobinuria, particularly Haff disease.

Death may result from respiratory failure (through skeletal-muscle damage, inhalation of vomit or secretions, and respiratory infection), hyperkalaemia, or acute renal failure. Even when these dangers are counteracted by treatment, death may occur.

In severe cases recovery may take up to six months and some of the clinical features resemble muscular dystrophy.

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