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Australian venomous jellyfish, envenomation syndromes, toxins and therapy

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Abstract

The seas and oceans around Australia harbour numerous venomous jellyfish. *Chironex fleckeri*, the box jellyfish, is the most lethal causing rapid cardiorespiratory depression and although its venom has been characterised, its toxins remain to be identified. A moderately effective antivenom exists which is also partially effective against another chirodropid, *Chiropsalmus* sp. Numerous carybdeids, some unidentified, cause less severe illness, including *Carybdea rastoni* whose toxins CrTX-A and CrTX-B are large proteins. *Carukia barnesi*, another small carybdeid is one cause of the 'Irukandji' syndrome which includes delayed pain from severe muscle cramping, vomiting, anxiety, restlessness, sweating and prostration, and occasionally severe hypertension and acute cardiac failure. The syndrome is in part caused by release of catecholamines but the cause of heart failure is undefined. The venom contains a sodium channel modulator. Two species of *Physalia* are present and although one is potentially lethal, has not caused death in Australian waters. Other significant genera of jellyfish include *Tamoya*, *Pelagia*, *Cyanea, Aurelia* and *Chyrosaora*.

1. Introduction

Australia is an island whose surrounding oceans are replete with numerous venomous creatures, including many species of jellyfish. Some are unique to Australian waters, while others are also to be found in distant oceans.

The study of the toxins of these creatures is in its infancy. Although, the lethality of some species of jellyfish in Australia had been long recognised by its indigenous people and from the 18th century by its colonists, very little is currently known about their toxins. Something is known about many venoms but few toxins have been identified.

Human envenomation occurs from all 4 classes (Hydrozoa, Scyphozoa, Cubozoa, Anthozoa) of the Phylum Cnidaria (formerly Coelenterata) which are characterised by possession of stinging cells, or nematocysts. While all have a sedentary polyp stage in their life cycles, 3 of the classes are often described as 'Jellyfish' because of their somewhat gelatinous free-floating medusal lifecycle stage. Of these, Scyphozoa are true jellyfish, Cubozoa are 'box jellyfish' but Hydrozoa are hydroids.

This review is of some current knowledge of the major Australian venomous jellyfish, their venoms and toxins, human envenomation syndromes and their medical treatment.

2. Box jellyfish, *Chironex fleckeri*

This is the most dangerous jellyfish and probably the most dangerous animal in the world. At least 63

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people had met sudden and painful deaths in subtropical Australian waters up to 1994 (Williamson et al., 1996). Since then, additional fatalities have included a 5-year-old child near Cairns and a 7-year-old boy stung at a beach off Tully on the Queensland coast. Many fatalities were of young children who died by combined circulatory and respiratory effects within minutes of being stung.

The creature responsible was identified in 1956 by Southcott who named it *C. fleckeri* in honour of Flecker who had spent many years investigating serious marine stings in Queensland waters (Southcott, 1956).

2.1. Distribution and seasonal incidence

The range of *C. fleckeri* has yet to be accurately defined. Endean (1981) reported that specimens had been found as far south as Port Curtis (latitude 24° south). The creature may be found from this area north along the whole of the Queensland coast and westward to Darwin and as far west as Exmouth in Western Australia (latitude 22° south: Peter Fenner, pers. commun. 2005). *C. fleckeri* probably inhabits the seas to the immediate north—a specimen from Vietnam is held in the South Australian Museum (Peter Fenner, pers. commun. 2005). Cleland and Southcott (1965) stated that deaths from jellyfish stingings have occurred from Bougainville Island through the Philippines and as far west as Penang. *C. fleckeri* is the jellyfish likely to have caused these fatalities although *Chironex quadrigatus*, a closely related multi-tentacled box jellyfish (chirodropid) may have been responsible. Fenner and Williamson (1996) reported another 14 deaths in Asian waters while Suntrarachun et al. (2001) reported a chirodropid sting related death in Thailand.

In Queensland the danger period is commonly regarded as October to May. Stings by *C. fleckeri* most commonly occur in December and January (Sutherland and Trinca, 1981; Fenner and Harrison, 2000) but only June and July have been sting free. In the Northern Territory and neighbouring islands stings have occurred in every month of the year with the peak prevalence in January (Fenner and Harrison, 2000).

2.2. Description and habits

C. fleckeri has a white or translucent cubic or box-shaped bell which may be as large as a 2-gallon bucket (i.e. 20×30 cm) and weigh more than 6 kg (Fig. 1). It is a highly advanced species. It has 4 sensory organs that contain eyes, vibration sensors and motion (gyration) sensors and is attracted to lights.

Hartwick (1987) established that it has used estuaries in autumn as breeding grounds and probably dies shortly after. The fertilised eggs develop into minute creeping polyps with two tentacles which attach to estuarine rocks. These sessile polyps may reproduce by budding. In spring the polyps metamorphose over 14 days and the immature jellyfish stage is carried to the open water of the river whilst developing as small medusae during migration back to the sea. Hartwick considered that 2–3 months later its size is sufficient to make it dangerous to humans.

The early life history of *C. fleckeri* was studied in culture vessels by Yamaguchi and Hartwick (1980). Once the eggs had been fertilised they no longer suspended freely, but stuck to each other or any solid matter. After progressing through 2 polyp forms, metamorphosis was seen in some polyps 58 days after spawning. Some medusae survived up to 7 weeks at which time they were 10 mm or more in width.

C. fleckeri propels itself along by ejecting water from its body cavity and it changes direction by altering the position of the cavity opening. The tentacles do not aid propulsion, but stream along behind. The usual rate of movement is less than 1 knot but if alarmed it can turn rapidly and perhaps reach a speed of 2 or more knots. The method of locomotion of *C. fleckeri* (and of other jellyfish) may be observed at 〈http://www.jcu.edu.au/interest/stingers/biology%201species%20page%202.htm#biologytop〉

On days that are hot, overcast but calm, *C. fleckeri* may move from the open sea into shallow water to pursue small prawns. Their quiet invasion of popular swimming spots may go unnoticed until some luckless swimmer brushes against their tentacles. Endean suggested that the speed of their appearance in shallow water after heavy seas had abated was due to the fact they had been waiting in readiness on the deep sea floor nearby. *C. fleckeri* has not been found in off-shore waters around coral reefs and is considered an in-shore or littoral species.

2.3. Structure and function of venom apparatus

Four bundles of up to 15 translucent extensile tentacles stream out from 4 pedalia (fleshy arms)

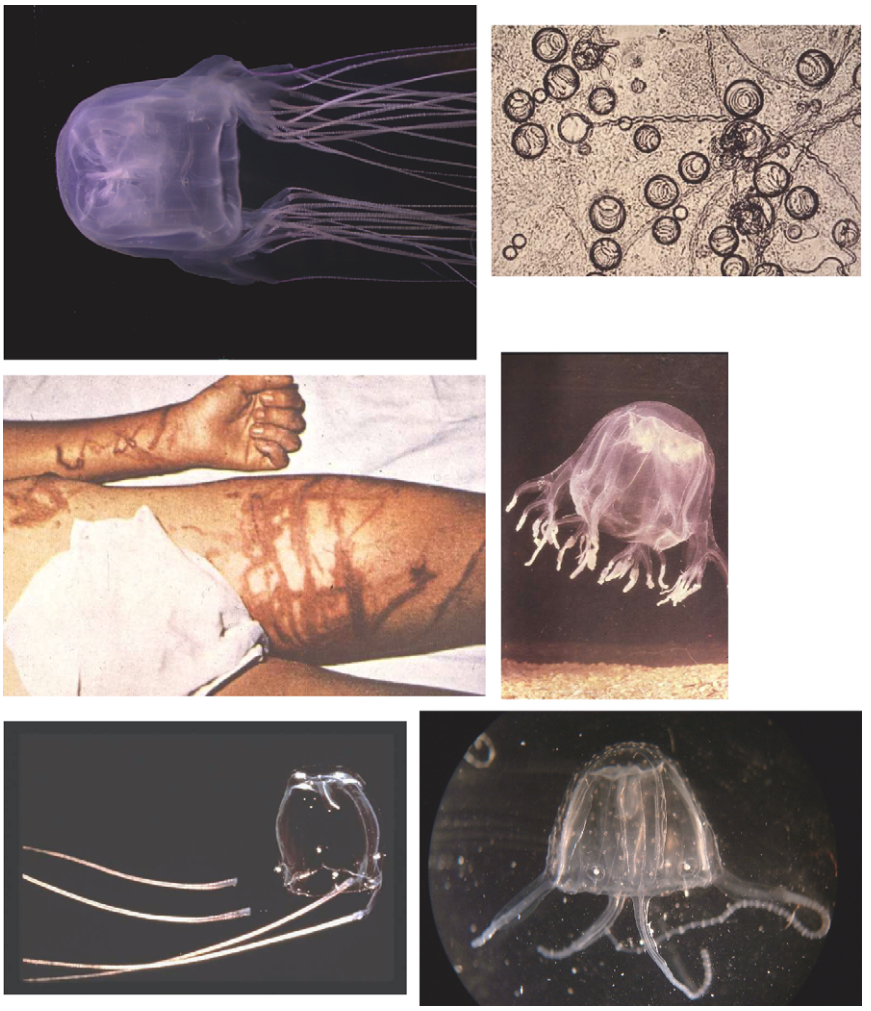

Fig. 1. Top panel: (left) Box jellyfish (*Chironex fleckeri*) (photo Lisa-Ann Gershwin); (right) Discharged and undischarged nematocysts, *Physalia utriculus* (from Cleland and Southcott, 1965). Middle panel: (left) Lesions from *Chironex fleckeri* sting (photo Dr J Barnes); *Chiropsalmus* sp. (photo K Gillett). Bottom Panel: (left) Jimble, (*Carybdea rastoni*) (photo N Coleman); (right) Irukandji, (*Carukia barnesi*) (photo Lisa-Ann Gershwin).

under the bell. There are no stinging capsules on the bell. The tentacles of mature specimens may stretch 3 m and they can contract to one-quarter of their length. In healthy specimens, the out-most tentacles may be bluish or purple and the inner tentacles tend to fade to a dirty greyish white (Barnes, 1965a). The wide ribbon-like tentacles are covered with millions of stinging capsules or nematocysts ('spring-loaded syringes'), which discharge fluid toxins via a penetrating thread or tube into the skin of any creature touching them. (Discharged and undischarged nematocysts of *Physalia utriculus* are illustrated in Fig. 1). The threads have little denticles which give the uncoiling thread cutting power like a diamond drill. The extruded thread may reach 1 mm long which is sufficient to reach into the dermis of human skin over most parts of the body. The stimulus for explosive release of the threads is not only physical contact since there appears to be remote as well as local control. It is postulated that the explosive release of the thread is caused by a sudden release of spring-like tensions stored in the collagenous structural compartment and by a sudden increase in the osmotic pressure of the capsular fluid, due to the removal of bound calcium ions (Lubbock and Amos, 1981; Tardent, 1995). The osmotic intracapsular pressure can amount to 150 bar. Another type of nematocyst contains a sticky substance which adheres the tentacle to the victim, while another acting like a

'grappling hook' pulls the tentacle closer to the victim, bringing into action 'batteries' of stinging cells, thus increasing envenomation the whole time adherent tentacles are in contact with the integument of their victim (Rifkin and Endean, 1983). The tentacles are easily torn off but their nematocysts remain active for long periods of time.

The nematocysts are packed into circular batteries which, when contracted, form alternating wide and narrow stinging bars. When Barnes (1967) used electrical stimulation to collect venom from tentacles, he found the maximum concentration of threads penetrating the membrane exposed to the tentacles to be greater than $1500/mm^2$. Barnes described how, if major stimulation is applied to a tentacle such as sudden traction, a discharge of nematocysts may occur along its whole length. In water this reflex discharge shows as a blurring of the profile of the tentacle and a sudden marked increase in width. If such a discharge is produced out of the water, 'the coating of whitish glistening threads looks like frost on refrigeration tubing.'

When the tentacles make contact with the jellyfish's normal prey, small fish or prawns, they contract thus bringing the struggling creature towards the bell and into contact with other tentacles. Thus the prey can quickly be immobilised by exposure to thousands of millions of poisonous threads. If the delicately built jellyfish could not quickly subdue its prey it would be damaged.

Rifkin and Endean (1983) proposed that toxic granular material on the outside of the tube or spine is released as the nematocyst discharges. Thus venom may be injected continuously and not only when the tube is fully everted. Venom would be washed off the tubes as they pass through capillaries and thus contribute to the rapidity of general effects in the victims.

2.4. Venom

2.4.1. Toxicity

Endean et al. (1969) demonstrated that extracts from nematocysts were highly toxic to prawns, fish, rats and mice. Prawns injected with the toxic extract of more than 50,000 nematocysts died within 5–90 s. When half of this dose was injected, prawns were paralysed for up to 41 min but recovered. Mice, which received the toxic yield from approximately 35,000 nematocysts, died within 2 min of intravenous injection. Freeman and Turner (1969) assayed toxin by intravenous injection in 20 g mice to determine a 'mouse unit.' Baxter and Marr (1969) determined accurate intravenous LD_{50} values in 25 g mice for their toxins. They estimated the intravenous LD_{50} dose for each species, expressed in mouse intravenous LD_{50}/kg, as: mouse 40; guinea pig 8; rabbit 2–8 and sheep 6. The LD_{50} for monkeys of 2 kg was found to be 50 mouse intravenous LD_{50} doses (Baxter and Marr, 1975). Most animals injected with a lethal dose died within 15 min. Control would be lost over the hind limbs and then the fore limbs. Respiration soon ceased and later cardiac standstill occurred.

It was found that mice tolerated large doses of venom by the intraperitoneal, subcutaneous or intradermal route without a fatal outcome (Baxter et al., 1968). Baxter et al. (1973) studied the lethal effects of the venom in rabbits, sheep and monkeys and concluded that the abrupt deaths seen were similar to those described in humans.

2.4.2. Venom preparation

Collection of venom from jellyfish is difficult. Interpretation of findings concerning the characteristics and actions of the toxin(s) has been subject to the mode of toxin collection. Several techniques have been used. Preliminary studies were carried out by Wiener who examined extracts of frozen tentacles and showed that they had haemolytic, dermatonecrotic and lethal activity (Southcott and Kingston, 1959). These findings were confirmed and amplified by Baxter and Marr (1969), using 'milked' venom. They showed that the different activities of the venom were due to separate and labile protein components.

Barnes (1967) was the first to obtain venom by 'milking'—a technique in which venom is harvested from tentacles applied to an amniotic membrane and electrically stimulated. Freeman and Turner (1969) made extractions from tentacles, which had been stored in liquid nitrogen, and Endean et al. (1969) froze the tentacles with dry ice, removed the nematocysts and then extracted the venom from the latter. Keen (1971) simply extracted venom from homogenised tentacles to obtain the most active preparation. Although extracts may contain substances which are not found in venom, the chromatographic profiles of both preparations and of their biological effects were similar (Freeman and Turner, 1969; Crone and Keen, 1971) thus enabling at least fair comparison of studies.

Bloom et al. (1998) severed tentacles from specimens at the beach and allowed them to autolyse in

refrigerated sea water for up to 4 days. Each day the suspension was vigorously shaken. The sediment was collected, lyophilised and shipped for experimentation. Microscopic examination of the resuspended material showed a relative lack of tentacular debris and a concentration of unruptured nematocysts. Prior to analysis of venom, the nematocysts may be ruptured by sonication (Bloom et al., 1998) or by bead mill beater (Carrette and Seymour, 2004).

2.4.3. Haemolysin

The haemolytic component (haemolysin) was studied by Keen and Crone (1969a), and by Crone and Keen (1969, 1971) who confirmed it to have a molecular weight of about 70 kDa. Crone (1976a) found that the haemolysin contained a disulphide bond which was essential for its activity. Haemolysis could be prevented by the presence of either divalent cations or trace amounts of ganglioside but later the interaction of the haemolysin with gangliosides was found to be non-specific in nature (Crone, 1976b). No phospholipase A or C activity was found in the venom by Crone (1976a). Extracts of nematocyst intracapsular material exhibited haemolytic activity but had no phospholipase A or proteolytic activity (Endean and Henderson, 1969). Further studies of extracts of isolated nematocysts and of tentacles from which nematocysts had been removed confirmed the presence of a haemolytic agent of molecular weight 70 kDa (Endean et al., 1993). Tibballs et al. (1998a) concluded that haemolysis was caused by infusion of extracts of tentacles because of elevated free haemoglobin levels in experimental animals.

Although haemolysis may be of some significance in experimental situations, it has not been observed in clinical situations. However, no systematic clinical study of haemolysis has been conducted.

2.4.4. Dermatonecrotic component

The dermatonecrotic factor isolated from the venom produced rapid skin death in experimental animals, the changes being similar to those seen in human skin (Freeman and Turner, 1969; Keen, 1970). Injection of this necrotrizing fraction did not produce pain and it was free of histamine and 5-hydroxytryptamine.

2.4.5. Lethal component and mode of action

Although subject to considerable investigation, the identity of this component and precisely how its actions are exerted remain unknown. Generally acknowledged to be a protein(s), it has been difficult to investigate because of its ability and tendency to aggregate, disaggregate, bind to non-toxic components and to adhere to apparatus (Olson et al., 1984). Crone and Keen (1969, 1971) found that a lethal component was a labile protein of molecular weight about 150 kDa but other workers (Baxter and Marr, 1969; Olson et al., 1984; Othman and Burnett, 1990; Naguib et al., 1988) have suggested a lower molecular size. The component is known to lose much of its biological activity if exposed to proteolytic enzymes (Marr and Baxter, 1971).

Extensive studies by Endean et al. (1969) of the biological activity of nematocyst extracts revealed that, in envenomated experimental animals, the heart progressively failed to relax and became paralysed in systole. Freeman and Turner (1969) showed that respiratory arrest of apparently central origin was the terminal event in all species studied but clear evidence of cardiotoxicity was also obtained. Bradycardia developed, with varying degrees of conduction delay, and terminal atrioventricular block usually occurred. Biphasic blood pressure changes were seen and blood samples, taken before terminal apnoea developed, had varying degrees of haemolysis and raised serum potassium. Further work by Freeman and Turner (1971, 1972) suggested that the cardiovascular picture produced by cardiotoxicity and vasoconstriction might be complicated by baroreceptor stimulation.

Multiple lethal toxins are probably present in venom or single toxins may have multiple actions. Endean (1987) isolated 2 myotoxins of approximate MWs 150 and 600 kDa from crude nematocyst venom. The toxins contracted skeletal, smooth and cardiac muscle (Endean, 1987; Endean and Sizemore, 1987). In additional work, Endean et al. (1993) isolated a haemolysin of approximate MW 70 kDa and showed that the myotoxins were composed of aggregations of subunits of approximately 18 kDa MW. Working with extracts of tentacles from which nematocysts had been removed, a haemolysin and a neurotoxin of approximate MW 150 kDa were isolated. All 5 toxins were lethal to mice on intravenous injection. Calton and Burnett (1986) isolated 2 components from a tentacle extract by immunochromatography using antivenom. They confirmed a lethal factor had a molecular weight of 150 kDa. Naguib et al. (1988) generated monoclonal antibodies against tentacle

extract which suggested the presence of at least 2 haemolysins, 2 dermatonecrotic and 3 factors lethal to mice. Collins et al. (1993) generated 3 monoclonal antibodies against haemolytic activity of tentacle extract.

Bloom et al. (1998), working with lyophilised but undestroyed nematocysts obtained by 'beachside' autolysis of tentacles, was not able to demonstrate the existence of the 600 kDa toxin previously identified by Endean (1987) and by Endean et al. (1993). Instead, native polyacrylamide gel electrophoresis of crude venom yielded protein bands of MW 30–200 kDa, which lost activity with freeze-thaw cycles.

The extreme rapidity of action of the venom is explained at least in part by its probable intracapillary delivery (Rifkin and Endean, 1983). Cellular death may be the result of calcium entry but the evidence does not favour direct activation of calcium channels (*infra*). In other species, e.g. *Physalia physalia*, calcium influx appears to be the result of toxin-induced membrane pore formation (Edwards and Hessinger, 2000; Edwards et al., 2000). This may also be the mode of action of *C. fleckeri* venom. Indeed, Bailey et al. (2005) observed by electron microscopy, the formation of large numbers of circular lesions in the membranes of rat myocytes after exposure to *C. fleckeri* venom.

2.5. Envenomation

C. fleckeri is rarely noticed by the victim until contact has been made with the tentacles and even then it may not be seen. Stings usually occur to victims who are wading or swimming in quite shallow water. The tentacles are easily torn from the jellyfish by the encounter and in adhering to the skin of the victim, resemble earthworms of a pink, grey or bluish hue. Stings from small *C. fleckeri* are incapable of penetrating adult skin of average thickness, but may cause weals on infants or on thin adult skin, for example, between the fingers (Barnes, 1960). Specimens which have a bell of 5–7 cm in diameter can cause painful local changes which may persist for several days. However, if a larger creature is involved, say with a bell wider than 15 cm, the result may be extremely severe.

Barnes (1960) described the unmistakable features of stinging as follows: 'Stings from large Cubomedusae (15 cm or more across the top of the bell) are extremely severe. During the first 15 min pain increases in mounting waves, despite removal of the tentacle. The victim may scream and become irrational. Areas of contact are linear and multiple, showing as purple or brown lines often compared to the marks made by a whip. A pattern of transverse bars is usually visible. Wealing is prompt and massive. Oedema, erythema and vesiculation soon follow, and when these subside (after some 10 days), patches of full-thickness necrosis are leaving permanent scar perhaps with pigment changes.'

Severity of injury is related to size of the jellyfish and the extent of tentacle contact. Most stings are quite minor. O'Reilly et al. (2001) prospectively studied victims of jellyfish sting presenting to The Royal Darwin Hospital. Over a 12-month period 1999–2000, of 40 victims, 28 were due to *C. fleckeri* as determined by identification of nematocysts sampled by sticky-tape applied to the sting site. None of these were life-threatening and none required antivenom. Stings from specimens with a bell diameter of 15 cm or more are severe (Barnes, 1960). Death is probable if the total length of weals on the victim is greater than 6 or 7 m (Barnes, 1966). Death may occur within minutes of the stinging (Cleland and Southcott, 1965). In severe cases, consciousness is lost, perhaps mercifully, within seconds of the injury.

The mechanism of death in humans is not known with certainty but on the basis of case reports it is probably a consequence of combined cardiovascular and respiratory effects. Several reports describe the onset of apnoea (Maguire, 1968; Williamson et al., 1980) while others suggest severe hypotension as the primary event (Lumley et al., 1988; Beadnell et al., 1992). Some experiments conducted in animals clearly showed apnoea and cardiovascular effects (Freeman and Turner, 1969, 1971, 1972) but these were conducted during spontaneous ventilation making it difficult to determine whether apnoea or hypotension was the primary effect. However, there is little doubt that cardiac effects are prominent since tentacle extract administered to mechanically ventilated piglets caused severe hypotension, cardiac dysrhythmias and pulmonary hypertension (Tibballs et al., 1998a) while mechanical ventilation did not influence cardiovascular collapse caused by nematocyst-derived venom in rats (Ramasamy et al., 2004).

The immunological aspects of *Chironex fleckeri* envenomation, and indeed of other species in Australia, have been given very little attention in contrast to other non-Australian species (Burnett et al., 1996). However, of 19 victims of *C. fleckeri*

envenomation, 11 (58%) had delayed hypersensitivity reactions which resolved spontaneously or with oral antihistamine and topical corticosteroid (O'Reilly et al., 2001).

2.6. Differential diagnosis

The lesions caused by *Chironex fleckeri* are distinctive. The skin is heavily marked, usually in a criss–cross fashion, with transversely barred weals which may be 8–10 mm wide (Fig. 2). These 'frosted ladder patterns' match the bands of nematocysts on the tentacles. Lesions produced by the other highly dangerous jellyfish, *Chiropsalmus quadrigatus* are narrower and milder and the tentacular area is far less than that of *C. fleckeri,* which Barnes (1966) estimated produced 100–200 times more venom. Sometimes, a similar injury is attributed to another species on the basis of the known range of *C. fleckeri:* Bengston et al. (1991) thus attributed a fatality in the Gulf of Mexico to *Chiropsalmus quadrumanus.*

2.7. Antivenom

Chironex fleckeri antivenom is the only jellyfish antivenom manufactured Worldwide and has been in use since 1970 (Winkel et al., 2003). Keen and Crone (1969b) observed that tentacle extract and 'milked' venom were antigenic in rabbits. The antisera effectively reduced lethal and haemolytic effects and to a lesser extent the dermatonecrotic effects in rodents. It has efficacy in treatment of *Chiropsalmus* sp. stings (see below). An experimental vaccine was prepared by Baxter and Marr (1975) but was never used in humans.

Antivenom consists of concentrated immunoglobulins isolated from the serum of sheep which have been hyperimmunised with *C. fleckeri* venom. Each ampoule contains sufficient activity to neutralise 20,000 intravenous LD_{50} mouse doses. Baxter and Marr (1974) showed in vitro that the ovine antivenom (raised against 'milked' venom) neutralised the lethal, haemolytic and dermatonecrotic effects of tentacle extract and of 'milked' venom. Endean and Sizemore (1988) observed that this antivenom was less effective against crude nematocyst venom than against 'milked venom' thus implying that venom prepared from nematocysts contained more or additional toxins compared with 'milked' venom. Burnett et al. (1990) observed that the antivenom reduced mortality in mice injected with tentacle extract. Tibballs et al. (1998a) observed that the antivenom incubated with tentacle extract prevented haemolysis and systemic hypotension but not pulmonary hypertension in mechanically ventilated piglets. Ramasamy et al. (2003) observed that antivenom mixed with venom neutralised neurotoxic effects but not myotoxic effects in a chick biventer nerve-muscle preparation. Established neurotoxic effects however were not reversed by antivenom in that study. Antivenom administered 10 min before envenomation prevented cardiovascular collapse in only 40% of anaesthetised rats leading the investigators (Ramasamy et al., 2004) to suggest that the venom used to raise antivenom may be lacking a lethal factor.

Numerous components in tentacle extracts are antigenic (Keen and Crone, 1969b; Naguib et al., 1988; Collins et al., 1993). Reactions to antivenom appear infrequent. One patient who survived respiratory arrest developed a mild generalised rash 20 min after antivenom (Sutherland and Lovering, 1979). Antibodies raised against venom components may be used to diagnose the species responsible for an otherwise unknown jellyfish sting (Burnett et al., 1988).

Antivenom use is not frequent but no doubt vital. It was used in 38 cases in Queensland between 1970 and 1978 (Sutherland and Trinca, 1981) with the average age of the victim of 14 years and a median age of 11 years. In a later analysis by Wendy Cowling from 1970 to 1981 (Sutherland and Tibballs, 2001), 73 patients had received antivenom: 45 in Queensland; 27 in Northern Territory and 1 in Western Australia. Cases had occurred in every month except August with the most frequent in December and January. Sutherland (1992) reported that six cases of antivenom usage were received by CSL Ltd between November 1989 and April 1990. All were stung in the Northern Territory and had suffered excruciating pain and life-threatening systemic effects. Some had vinegar applied immediately. No patient had an immediate reaction to the intravenous administration of antivenom, and no delayed reactions were reported in the 4 which were successfully followed up. Hawdon (1998) found the only 6 cases of use between January 1994 and October 1997 but since reporting is not compulsory the true use is unknown.

2.8. Management of envenomation

The severity and rapidity of envenomation after a sting mandate decisive action on the beach, during

transport and in hospital. The mainstays of management are:

- First-aid: Retrieval of victim from the water to avoid further contact with the creature(s) and to prevent drowning; basic life support; Inactivation of undischarged nematocysts by pouring vinegar (4–6% acetic acid) over adhering tentacles for at least 30 s. (Alcohol in any form must not be used for this purpose.)
- Advanced cardiopulmonary resuscitation on the beach wherever possible, during transportation and in hospital.
- Administration of antivenom according to circumstance.

2.8.1. Dousing with vinegar

For many years the recommended first aid for *C. fleckeri* stings was to pour any form of available alcohol, usually methylated spirits, over the adhering tentacles. The rationale was that the dehydrating effect of the alcohol prevented the movement of fluid into the nematocysts of fluid, which was thought to be the mechanism precipitating their discharge (Mariscal, 1974). However, Hartwick et al. (1980) following a chance observation, noted that the immersion of a piece of living tentacle in methylated spirits caused immediate large-scale nematocyst firing! They produced evidence that the simplest and most economic first-aid procedure was to douse the tentacles with domestic vinegar. Once treated by vinegar, the nematocysts could not be triggered even by exposure to alcohol.

Of all the substances tested by Hartwick et al. (1980) only vinegar or acetic acid in solutions 3–10 per cent produced rapid and complete inhibition, as tested by later exposure to methylated spirits. A 10 per cent formalin solution produced inhibition but it was slow. The commercial preparation 'Stingose' (Hamilton Labs), which contains 20 per cent aluminium sulphate (Henderson and Easton, 1980), did not inactivate the nematocysts as well as vinegar. Of interest is the observation by Thomas et al. (2001a) that Sting-Aid (an aluminium sulphate solution) was no better than seawater in altering the pain of the Hawaiin 'box jellyfish' *Carybdea alata*. The use of vinegar for jellyfish stings has been long known elsewhere. Light (1914) recorded that natives of the Philippines applied a mixture of vinegar and sugar to severe jellyfish stings.

Vinegar-treated tentacles may be removed with safety. However, this is not necessary and consumes valuable time. If vinegar is not available, the tentacles may be picked off safely by rescuers since only a harmless prickling may occur on the fingers of the rescuer (Williamson et al., 1996). Detached live tentacles should be treated with caution. An unwitting 19-year-old lifesaver ostensibly experienced pharyngeal oedema and respiratory difficulties when he mistakenly drank from a bottle containing tentacles collected for research. (*The Age*, Wednesday 5 January 2000).

2.8.2. Use of first-aid pressure-immobilisation bandage

This is a controversial issue (Little, 2002). Originally this technique was adopted from the management of elapid snake bite where it retards the movement of venom from the bite site via lymphatic channels (Sutherland et al., 1979). However, application of pressure simulating a pressure-immobilisation bandage caused in vitro discharge of additional venom from partially discharged *Chiropsalmus* sp. nematocysts (Pereira et al., 2000) and from vinegar-soaked *Chironex fleckeri* nematocysts (Seymour et al., 2002). The possible advantage to be gained by retarding central movement of venom by compression of lymphatics or small blood vessels or both against the possible harm of inducing additional envenomation has yet to be tested in a realistic model of jellyfish envenomation (Fenner et al., 2001; Tibballs et al., 2001). Until evidence is presented which clarifies the situation, the Australian Resuscitation Council (2002) has recommended that first-aid treatment be confined to basic life support, dousing of the affected area with vinegar and rapid transport of the victim to hospital. If a pressure-immobilisation bandage is to be used it should not be applied unless vinegar has been applied first and not if it interferes with other treatment. Although arterial tourniquets have been used in the past, they are no longer recommended.

2.8.3. Indications for antivenom

Antivenom should be administered as soon as first aid is applied. It should be given to a victim of suspected *C. fleckeri* stinging in the following circumstances:

- Unconsciousness, cardiorespiratory arrest, hypotension, dysrhythmia or hypoventilation.
- Difficulty with breathing, swallowing or speaking.

- Severe pain (parenteral analgesia is also usually required).
- Possibility of significant skin scarring.

The dose recommended by experienced clinicians is 3 ampoules (intravenously) (Currie, 1994; Williamson et al., 1996). One or 2 ampoules have not prevented death (Lumley et al., 1988; Currie, 1992) although such therapy was unavoidably delayed in relation to the rapidity of envenomation. More than 3 ampoules may be required on theoretical grounds (Endean and Sizemore, 1988). Antivenom should be given as soon as possible. Two or 3 ampoules may be required to alleviate pain or to prevent scarring (Boyd, 1984; Williamson et al., 1984; Horne, 1988; King, 1991).

Antivenom should be injected intravenously, preferably by infusion. A dilution of 1 in 10 is advisable. The risk of serum reactions normally precludes the use of antivenom by lay persons but, if an emergency arises remote from medical aid, intramuscular injection by an informed layperson is justifiable. Indeed, several cases of severe envenomation have been treated successfully with intramuscular antivenom administered by trained ambulance personnel on the beach (Fenner et al., 1989; Beadnell et al., 1992). In such circumstances 3 ampoules should be administered remote from the sites of envenomation or proximal to pressure-immobilisation bandages.

The antivenom is considered to be effective in reducing pain and local tissue damage provided it is given early. Williamson et al. (1984) reported 2 cases with remarkably dramatic relief of pain with antivenom. One patient had no relief with pethidine and the other responded neither to topical lignocaine nor iced water. In the latter case the skin lesions were seen to improve within 90 s of the antivenom. Dramatic pain relief in an infant was reported by Boyd (1984). Topical corticosteroid or oral antihistamine (O'Reilly et al., 2001) or systemic steroids reduces the swelling and itchiness of the skin lesions. Indomethacin and methysergide reduced experimentally induced capillary leakage (Burnett and Calton, 1986).

2.8.4. Laboratory diagnosis

The simplest and quickest way to confirm *Chironex* envenomation is to examine microscopically a 4–8 cm long piece of ordinary transparent sticky tape applied to the sting site. The tape is applied to a lesion, stroked several times, removed and with its sticky side up affixed onto a glass slide with other pieces of tape. This method was more successful than using skin scrapings to identifying characteristic *Chironex* nematocysts in patients presenting to The Royal Darwin Hospital with jellyfish stings (Currie and Wood, 1995).

Microscopic examination of scrapings from the skin or sections of lesions may also confirm the diagnosis of jellyfish stinging. Skin scrapings may be suspended in sea water or saline and allowed to dry out on glass slides. Examination of these scrapings may determine the origin of the nematocysts, but it is difficult to distinguish between those of *C. fleckeri* and *C. quadrigatus*. The undischarged nematocysts of these 2 jellyfish are both long and narrow ($100\,\mu \times 20\,\mu$) and are clearly different from other medically important jellyfish (Barnes, 1960; Rifkin and Endean, 1983). Barnes described the nematocysts of *Physalia physalis* as circular with a diameter of 20 μ and those of *Cyanea capillata* as being rod-like with dimensions of $25\,\mu \times 5\,\mu$. If silver impregnation methods are used, penetrating nematocyst threads are seen. The toxin causes oedema of the stratum corneum and death of cells. The histopathology of the skin changes are comprehensively described by Kingston and Southcott (1960), Cleland and Southcott (1965) and Williamson et al. (1996).

2.8.5. Calcium channel blockade

The use of verapamil, a calcium channel blocker, has been advocated in the management of serious *Chironex* envenomations (Burnett and Calton, 1983; Burnett et al., 1990; Williamson et al., 1996) but it may prejudice otherwise successful treatment of serious envenomation. No successful clinical uses have been reported and combined evidence from animal studies contraindicates its use.

Chironex envenomation may be acutely life-threatening and in this desperate setting the basis for considering the use of calcium channel blockade at first appears logical since experimentally venom causes vasoconstriction (Freeman, 1974), decreases coronary blood flow, heart rate and amplitude of contraction in isolated perfused hearts (Turner and Freeman, 1969). Moreover, venom preparations caused an influx of calcium ions into muscle fibres (Endean and Henderson, 1969), inhibited uptake of calcium by the sarcoplasmic reticulum (Endean and Henderson, 1974) and interfered with electrical events and contraction of myocardial tissue (Freeman, 1974). All these events were assumed to

be primarily due to opening of calcium channels, but the evidence is questionable.

Mustafa et al. (1995) confirmed that application of toxin to papillary muscle and isolated myocytes resulted in an increase in intracellular calcium and adverse symptoms of calcium overload (aftercontractions, spontaneous contractions, a decrease in developed force and an increase in resting force). However, these events were all secondary to the influx of Na^+ into cells and importantly were not blocked by prior exposure to nifedipine, another calcium channel blocker. Neither were they prevented by exposure to Na^+ channel blockade, by inhibitors of sarcoplasmic reticulum, Na^+/K^+ ATPase or Na^+/H^+ exchange. The reponses of the toxin were however blocked by prior exposure to solutions which contained no Na^+ and by Ni^+. Interestingly, another group of researchers (Kleiman et al., pers. commun. 1988) had also observed that toxin induced contraction of myocytes was not blocked by calcium channel blockers (verapamil, cadmium) or by the sodium channel blocker tetrodotoxin but were blocked in sodium-free and calcium-free solutions. Voltage clamp studies suggested that the toxin had no direct effect on the calcium channel but instead enhanced permeability to sodium which induces calcium overload via Na–Ca exchange. They supported the proposal by Olson et al. (1984) that *C. fleckeri* toxin inserts into the myocyte sarcolemma and acts as a monovalent ionic channel. This echoes a previous similar suggestion by Freeman (1974) after observation that venom increases sodium conductance of cardiac cell membranes which is reversed by the sodium channel blocker tetrodotoxin. Recently, Bailey et al. (2005) observed that *C. fleckeri* venom causes a large elevation of cytosolic Ca^{++} in rat myocytes which is not prevented by verapamil but which is prevented by the transitional metal lanthanum (La^{3+}), a non-specific channel and pore blocker.

Verapamil may be useful against the effects of venom on smooth and skeletal muscle. When applied before or after crude nematocyst venom, it blocked contraction of strips of ileal muscle but had no effect in blocking diaphragm contraction induced by crude venom. It did however block diaphragm contraction induced by a subfraction of crude venom (Endean and Sizemore, 1987).

The efficacy of verapamil has been tested in vivo as a prophylactic (before envenomation) or rescue treatment (after envenomation). Burnett and Calton (1983) observed that verapamil administered 2–3 s after venom (1.25 lethal doses) did not prevent death but prolonged the time to death in mice. Although verapamil was ineffective when given before the same dose of venom, it was effective against larger doses in prolonging time to death but it did not prevent death. This work was criticised for methodological flaws (Freeman, 1984).

Endean and Sizemore (1987) performed similar experiments in mice with venom and venom fractions prepared from nematocysts. In these, early death within 2 min was attributed to irregular cardiac activity while death after 6–7 min was attributed to pulmonary oedema and respiratory difficulties. Death was not prevented nor was time to death prolonged by administration of verapamil 5 min prior to envenomation. Likewise death was not prevented or time to death prolonged by administration of verapamil 2 min after envenomation. Indeed time to death was shortened, but not significantly, in both prophylactic and rescue experiments. Similar observations were made with subfractions (T_1, T_2) obtained by chromatography and ultrafiltration although time to death was prolonged in mice treated with prophylactic verapamil before fraction T_1.

Subsequent experiments on the efficacy of rescue verapamil and antivenom were carried out by Burnett et al. (1990). In these, survival was increased from 0 to 27 per cent with verapamil, 32 per cent with antivenom and to 65 per cent with both verapamil and antivenom. The times to death were prolonged with verapamil but these results were criticised for use of different preparations of venom in different parts of the experiments and unexplained exclusion of some animals from statistical analysis (Tibballs et al., 1998b). In none of the above experiments were the cardiac and respiratory effects examined separately. Rescue experiments with verapamil and antivenom were repeated with venom prepared from isolated lyophilised nematocysts in which verapamil was claimed to enhance the survival time of mice previously injected with 2 LD_{50}s of venom (Bloom et al., 1999), but presumably not survival. However, the results were not convincing: antivenom alone failed to increase survival time in 3 antivenom dose schedules (0.15, 1.0 and 3.4 anti-lethal units/g) while antivenom in 3 dose schedules (0.15, 0.3 and 3.4 anti-lethal units/g) plus verapamil 1 μg also failed to increase survival times compared with venom alone. Antivenom in 1 dose, 1.0 anti-lethal unit/g, that is at a dose

intermediate between doses that failed, plus verapamil 1 μg did significantly prolong survival. This observation was rationalised by postulating that an optimal dose of antivenom with verapamil was required to enable longer survival. The effect of verapamil alone was not reported.

Tibballs et al. (1998a) examined the cardiac effects of tentacle extract and verapamil and antivenom in closely monitored mechanically ventilated anaesthetised piglets, thus excluding possible complications of ventilation failure. They observed that verapamil, in the maximum dose which did not depress blood pressure, did not prevent hyperkalaemia or any of the cardiovascular effects of venom (cardiac output diminution, hypotension, dysrhythmias or pulmonary hypertension) given in equal doses alone. Importantly, verapamil also increased mortality from zero, observed with equal doses of venom alone, to 100 per cent. The dysrhythmias observed with higher fatal doses of venom alone were ventricular fibrillation, ventricular tachycardia and slow idioventricular rhythm with pronounced conduction block. Similar dysrhythmias were observed in animals pre-treated with verapamil and smaller doses of venom. No rescue experiments were performed. It was concluded that verapamil is not an effective prophylactic agent. The hyperkalaemia observed in these experiments was probably due at least in part to haemolysis since high concentrations of plasma haemoglobin were measured. Destruction of other cellular membranes may also occur as observed with *Physalia* venom (Edwards et al., 2000; Edwards and Hessinger, 2000) enabling release of potassium.

The ineffective and indeed deleterious cardiovascular effects of verapamil were confirmed in vivo and in vitro by independent research groups. In rats, verapamil in the maximally tolerated dose, did not alone have any effect on venom-induced cardiovascular collapse (Ramasamy et al., 2004). Moreover, verapamil negated the partially protective effects of antivenom. Bailey et al. (2005), investigating the role of calcium channels with venoms of *C. fleckeri*, *Chiropsalmus* sp. and *Carybdea xaymacana*, observed that verapamil had no effect on venom-induced calcium influx into myocytes. They concluded that there was no evidence that the venom of *C. fleckeri* exerted its effect by L-type Ca^{2+} channels.

Thus on an overall evidentiary basis, verapamil cannot be recommended as cardiac therapy for the seriously envenomated patient. Indeed, it is harmful and contra-indicated. It has been useful as an aid to understand the mode of action of venom, but it is not in this circumstance a therapeutic agent. The well-known hypotensive action of this drug by its vasodilator and negative inotropic effects would prejudice resuscitation. In addition, it is not recommended by authoritative resuscitative organisations for the treatment of life-threatening dysrhythmias in adults or children (International Liaison Committee on Resuscitation, 2005). Other treatments are recommended for hypotension and dysrhythmias.

If indeed calcium channel blockade has a role in the therapy of envenomation, a calcium channel blocker of the T-type with less negative inotropic action would be more appropriate. T-type channel blockade however in experiments with *Physalia* venom, did not prevent influx of calcium in *Physalia* experiments and whereas transitional metals successfully prevented calcium influx the cytolytic effects of the venom were not prevented (Edwards et al., 2000). These and the earlier experiments suggest that calcium influx in jellyfish envenomation is a phenomenon secondary to sodium channel activation. Clearly, more research with *Chironex fleckeri* venom is required to understand the actions of the venom and to treat envenomation. While verapamil may have a role in research, its role in clinical management of envenomation is non-existent.

2.8.6. Magnesium

Magnesium may be an important adjunctive therapy in envenomation. Prophylactic administration of magnesium alone did not prevent cardiovascular collapse induced by venom in rats but improved the effectiveness of antivenom from 40 per cent to 100 per cent (Ramasamy et al., 2004).

2.8.7. Skin medications

Apart from vinegar no topical agents (anaesthetic or steroid preparations) have been considered to be efficacious in case reports. Methylated spirits and ethanol cause nematocyst discharge and should not be used. If vinegar is not available, then Coca cola or old wine (which have pHs similar to vinegar) but not urine (a traditional treatment) has been used with moderate beneficial effect, although nowhere near as efficient as vinegar (Currie et al., 1993).

2.8.8. Ice packs

The majority of mildly painful stings respond well to application of ice packs (Currie, 1994) after the application of vinegar.

2.8.9. Application of heat

This has not been investigated scientifically for box jellyfish stings in Australian waters. However, in Hawaii, hot showers appeared to be analgesic for victims of Irukandji syndrome (Yoshimoto and Yanagihara, 2002) while hot-water immersion of *Carybdea alata* stings was better than applications of vinegar or papain meat tenderiser (Nomura et al., 2002). A randomized placebo-controlled trial of the analgesic effect of hot and cold packs on stings caused by *Carybdea alata* in Hawaii showed a minimal trend toward pain relief after 10 min of hot pack application (Thomas et al., 2001b). It has long been known that heat inactivates jellyfish venoms, most recently demonstrated with *C. fleckeri* venom by Carrette et al. (2002) using temperatures up to 58 °C—which is impractical for human treatment. However, immersion of *Physalia* stings at 45 °C does provide relief (Loten et al., 2006).

2.8.10. Prevention

People should never swim in the subtropical waters of Australia (beaches, estuaries) when a 'jellyfish alert' has been issued. They should not even wade or paddle in the water on such days. Swimming should be restricted to the safe months of the year and to beaches enclosed by jellyfish resistant nets ('stinger enclosures'). If the water must be entered because of a person's occupation or hobby, then protective clothing should be worn. Wet suits and gloves are ideal, but body stockings, overalls or old clothing give good protection. Special 'stinger suits' are highly recommended. As a general rule swimming should be confined to beaches patrolled by life savers. It is unwise to wade or swim alone on remote beaches. The tragic results of so doing are reflected in the deaths of young children.

3. Other chirodropids

In addition to *C. fleckeri* several jellyfish with a box-shaped bell and multiple tentacles arising from the corners of the bell (order *Chirodropidae*) cause significant illness. After *C. fleckeri,* the next most dangerous jellyfish belong to the genus *Chiropsalmus.* They do not grow as large as *C. fleckeri.* Although the injuries produced are severe, no definite fatalities have been recorded in Australia. Of the three species in the genus *Chiropsalmus*, *Chiropsalmus quadrigatus, Chiropsalmus buitendijki* and *Chiropsalmus quadrumanus*, only the first named frequents in-shore waters of northern Australia. In fact *Chiropsalmus buitendijki* and *Chiropsalmus quadrumanus* can for practical purposes be ignored because of their extreme rarity (Barnes, 1965a). Nonetheless, *Chiropsalmus quadrigatus,* is a major cause of stings in the Indo-Pacific (Williamson et al., 1996) and *Chiropsalmus quadrumanus* elsewhere such as in Brazil (Haddad et al., 2002). The latter was also responsible for the death of a 4-year-old child in the Gulf of Mexico (Bengston et al., 1991) who died within 40 min of envenomation and the mechanism was consistent with acute cardiac failure with pulmonary oedema. Nematocysts retrieved from the skin were identified as belonging to *Chiropsalmus quadrumanus.*

3.1. Chiropsalmus sp. (Australian Chiropsalmus quadrigatus)

3.1.1. Distribution

Historically, difficulties in identification of *Chiropsalmus* species have lead to the attribution of *Chiropsalmus quadrigatus* to different species throughout the Indo-Pacific region (Rifkin, 1996). The Australian species has not been formally identified but in literature it is referred to as either *Chiropsalmus quadrigatus*, which is misnamed, or as *Chiropsalmus* sp. (preferred). Barnes (1966) considered that the (Australian) *Chiropsalmus quadrigatus* had a much narrower distribution than *C. fleckeri* and might only be found between Cooktown and Innisfail off the coast of Queensland. The Philippine *Chiropsalmus quadrigatus* is common in the Philippines and in other areas of the Indo-West Pacific where it has caused many fatalities (Williamson et al., 1996). None of the documented deaths in Australia due to chirodropids have been attributed to *Chiropsalmus quadrigatus* (Williamson et al., 1996).

Multi-tentacled chirodropids have been captured during the 'safe stinger seasons' of 1991–1993 off beaches of the Gove Peninsula on the north-east tip of Arnhem Land in the Northern Territory (Currie et al., 2002). Although the taxonomy remains unclear, it is distinct from *C. fleckeri* and closely resembles the Queensland *Chiropsalmus* sp. thus questioning the latter's known range. Contact with the tentacles during netting caused mild pain, redness and itching.

3.1.2. Description and habits

A mature Australian *Chiropsalmus quadrigatus* (*Chiropsalmus* sp.) is smaller and less robust than a

C. fleckeri with a maximum bell diameter of 100 mm (Fig. 1). Distinction from an immature *C. fleckeri* of comparable size would be difficult but certain features of the bell of *Chiropsalmus quadrigatus* allow it to be distinguished by the expert from *C. fleckeri*. These are the shapes of the pedalial canal, the perradial nuclei and the shape of the gonads (Barnes, 1965a, 1966). *Chiropsalmus quadrigatus* rarely has more than nine tentacles attached to each of the 4 pedalia (fleshy arms) and these tentacles are shorter, much finer and rounded rather than flat compared with those of *C. fleckeri*.

When seeking food (particularly, *Acetes australis*, shrimps they swim near the surface and on calm days may be found in very shallow water. To avoid turbulence on rough days, they seek the shelter of the depths and, for this reason, are less likely to be washed up on the shore. Barnes (1966) observed that populations of this jellyfish tended to be of a more uniform size within a particular swarm, whereas very large and small *C. fleckeri* often co-exist in the same area.

3.1.3. Venom apparatus

The tentacles carry bands of nematocysts with similar appearance and properties to those of *C. fleckeri*. Barnes (1966) estimated that, at comparable dimensions, the Australian *Chiropsalmus quadrigatus* had less than one-tenth the stinging potential of *C. fleckeri*. A fully mature *C. fleckeri* might have over 100 times the venom output of a mature *Chiropsalmus quadrigatus*. The stinging capsules of small specimens of either jellyfish are too minute to penetrate adult human skin of normal thickness.

3.1.4. Venom

Extracts of whole tentacles from the Australian *Chiropsalmus quadrigatus* were found by Keen (1971) to have similar lethal, dermatonecrotic and haemolytic activities as extracts from *C. fleckeri* tentacles. These extracts were less potent, but present in the same proportions. Mice receiving lethal doses of *Chiropsalmus quadrigatus* extract died later than those receiving *C. fleckeri* extracts, but the mode of death (cardiovascular failure and respiratory arrest) was virtually identical. Freeman and Turner (1972) found the toxicity in mice of extracts from the Australian *Chiropsalmus quadrigatus* was approximately one-sixth of a comparable *C. fleckeri* extract and the solution was less stable, but had basically similar cardiovascular effects. Venom extracted from nematocysts of *Chiropsalmus* sp. was neurotoxic and myotoxic when added to a chick biventer nerve-muscle preparation (Ramasamy et al., 2003) while in rats, the venom caused cardiovascular collapse which was not prevented by *C. fleckeri* antivenom, artificial respiration or by magnesium (Ramasamy et al., 2005).

A number of studies have been conducted on the venom of the Okinawan *Chiropsalmus quadrigatus*, which is probably a different species from the Australian species. At low concentration, crude venom increased contraction of cardiac and aortic smooth muscle in vitro but diminished contraction at high concentration possibly by increasing calcium influx (Sakanashi et al., 2002). Venom extracted from nematocysts caused acute cardiac failure when injected intravenously into anaesthetised rabbits (Koyama et al., 2003). Hypotension, reduced femoral artery blood flow and raised left ventricular end-diastolic pressure occurred with 0.2–5 μg/kg, and at high doses (10 μg/kg) caused cardiac arrest. Pre-treatment of the animals with diltiazem attenuated the usual cardiovascular changes suggesting that venom activates calcium channels. Similar results were observed in anaesthetised rats (Noguchi et al., 2005). Nagai et al. (2002) isolated a proteinaceous toxin (CqTX-A, 44 kDa) from Okinawan *Chiropsalmus quadrigatus* nematocysts, sequenced the cDNA encoding the toxin and deduced its 462 amino acid sequence. It had a 25.2% similarity to *Carybdea rastoni* toxins (CrTXs), was lethal to crayfish via intraperitoneal administration and caused haemolysis in sheep red blood cells.

3.1.5. Envenomation

Contact with the tentacles may produce sudden severe pain and shock, but the illness is usually mild compared with that which may be caused by *C. fleckeri*.

Although deaths have been attributed to this jellyfish in the Philippines (Light, 1914, Williamson et al., 1996) and Japan (Nagai et al., 2002), none have been documented in Australia where it is probably a different species.

After some minutes the skin lesions become less painful, but discomfort may persist for at least 24 h. Swelling and redness develop immediately and tissue breakdown may occur. Any pigmentation and scarring has usually faded by 8 weeks.

3.1.6. Differential diagnosis

Capture of the offending jellyfish is the only positive way a diagnosis may be made, as otherwise

it is difficult to distinguish from mild injury due to *C. fleckeri*. Skin scrapings may reveal nematocysts similar to those from either jellyfish.

3.1.7. Antivenom

Box jellyfish (*C. fleckeri*) antivenom has been shown in mice to effectively neutralise the lethal, haemolytic and dermatonecrotic properties of Australian *Chiropsalmus quadrigatus* venom (Baxter and Marr, 1974), and to prevent neurotoxic and myotoxic affects of *Chiropsalmus* sp. venom in vitro (Ramasamy et al., 2003) but not cardiovascular collapse in vivo (Ramasamy et al., 2005).

3.1.8. First-aid and clinical management

Treat as for *C. fleckeri* stings.

4. Carybdeids

Carybdeids (Order Carybdeidae, Class Cubozoa) are 'box' jellyfish in the sense that the bell is cubic shaped. From each corner arises an arm (pedalium) usually bearing a single tentacle in contrast to those of chirodropids which bear many tentacles. Detailed information on the different species of carybdeids may be found in Williamson et al., (1996). Carybdeids of medical importance in Australia include *Carukia barnesi* ('Irukandji'), *Tamoya* spp. ('Morbakka'), the 'Darwin Carybdeid' and *Carybdea rastoni* (the 'Jimble'). Others include *Carybdea sivickisi*, *Carybdea xaymacana* and *Tripedalia binata* (http://www.reef.crc.org.au/publications/brochures/Carybdeidjellyfish.htm)

4.1. The Jimble, Carybdea rastoni

4.1.1. Distribution

Carybdea rastoni is a 4-tentacled carybdeid jellyfish first discovered in St. Vincent Gulf, South Australia, but now known to have a very wide distribution in the Western Pacific Ocean, and most Australian waters. It is found as far north as Japan (Williamson et al., 1996). Numerous other small carybdeids inhabit Australian waters.

4.1.2. Description and habits

Carybdea rastoni is a small creature with a translucent body, usually not much greater than 2 cm across (Fig. 1). The maximum size is 3 cm in width and 5 cm in length (Williamson et al., 1996). The tentacles stretch out some 5 cm to perhaps 30 cm. When contracted, the tentacles are denser and hence easier to see than the bell which is almost invisible.

Carybdea rastoni tends to be found in swarms and usually rises to the warmer surface of the sea in the early morning and evening. It may occasionally be seen on the surface at times other than dawn or dusk, but only on days that are very overcast. It swims quite actively in an oblique fashion and often breaks the surface of the water to produce small ripples.

4.1.3. Venom

A partially purified toxin (pCrTX) from the tentacles of *Carybdea rastonii* (sic) contracted aortic strips which was attributed to release of endogenous catecholamines and to an influx of Ca^{2+} in smooth muscle (Azuma et al., 1986a). A portion of such contraction was attributed to release of prostaglandins and a direct effect on smooth muscle not dependant on Ca^{2+} influx (Ozaki et al., 1986). The toxin also contracted intestinal smooth muscle which was attributed to release of prostaglandins (Nagase et al., 1987). The partially purified toxin and purified proteins (CrTX-1, CrTX-II, CrTX-III) obtained from the tentacles aggregates platelets by increasing cation permeability permitting an influx of calcium (Azuma et al., 1986b, c).

Winkel et al. (2002a) also demonstrated in vitro that a crude venom extract contracted blood vessels, an action that was absent in Ca^{2+} free media, and which was reduced but not abolished by felodipine, nicardipine and by T-type and L-type voltage-operated calcium channel antagonists (mibefradil, verapamil). When infused in vivo, the venom extract caused increase in heart rate and blood pressure which were abolished by verapamil. However, the tachycardia and hypertension, in contrast to similar effects of *Carukia barnesi* venom (Winkel et al., 2005), was not associated with catecholamine release leading the investigators to speculate that an Irukandji-like syndrome sometimes caused by this jellyfish is secondary to direct Ca^{2+}-dependant actions on vascular tissues.

Nagai et al. (2000) isolated protein toxins CrTX-A and CrTX-B with respective molecular masses of 43 and 46 kDa from the nematocysts and tentacles of *Carybdea rastoni*. The 450 amino acid sequence of CrTX-A, localised primarily in nematocysts, was derived from cDNA which encoded both toxins. This toxin was fatally toxic to mice at 20 μg/kg (i.v.) and to crayfish at 5 μg/kg (i.p.) and caused inflammation when injected subcutaneously. The

toxins have some sequence similarity to toxins derived from *Chiropsalmus quadrigatus* (Nagai et al., 2002).

4.1.4. Envenomation

The tentacles bear ovoid nematocysts which average 28 by 16 μm. Stings by *Carybdea rastoni* are usually but not always immediately painful with lesions almost invariably linear and frequently 4 in number, ranging from 10 to 20 cm in length. Southcott subjected himself to a number of stingings by severed tentacles and described in detail the local changes he observed (Cleland and Southcott, 1965). In most cases, the pain is of moderate severity and lasts up to 2 h. Weals 3–12 mm in width develop and they are surrounded by a flare some 4 cm in radius. Some stings produce small blisters of varying size. The swelling resolves over several days, but usually some pigmentary changes are evident for at least 2 weeks after the stinging. Southcott could not recover nematocysts by scraping the region of self-inflicted stings so examination of a piece of tentacle may be necessary to confirm the diagnosis. He considered the stings would not effectively penetrate the thick skin of an adult's palm.

Tentacles, cut from living jellyfish, caused severe pain lasting from 10 min to 8 h when placed on forearms of 25 volunteers (Ohtaki et al., 1990). Erythema and weal appeared within minutes and subsided within 24 h–3 days. At 7–13 days after application of the tentacles, linear erythema and papulo-vesicular lesions with pruritus lasting a week and leaving slight pigmentation were observed in 15 of the volunteers. The histological findings of these flare-up lesions corresponded to those of allergic contact dermatitis.

4.1.5. First-aid and clinical management

As with other box jellyfish stings, domestic vinegar should be poured over the adhering tentacles (Fenner and Williamson, 1987). Alcohol should not be used for this purpose. Application of local anaesthetic ointment, such as lignocaine, may be warranted when lesions are extensive.

4.2. The Irukandji, Carukia barnesi

For many years people bathing near Cairns in Queensland suffered an unusual type of marine sting, which Flecker (1952) called 'Irukandji syndrome.' The latter derives from the name of an Aboriginal tribe which formerly inhabited the area around Cairns. The marine sting differed from others in that, although the stung area was moderately painful, local effects were not serious, but 1/2 h or so later a severe general illness often occurred. The likely jellyfish responsible was not discovered until 10 December 1961, when Barnes (1964) lay in wait on the sea floor the day after several 'type A' stings had occurred and collected a specimen after it 'forced itself upon my attention, swimming right across the glass of my mask.' Although a connection was made between the Irukandji syndrome and a jellyfish which was to become known as *Carukia barnesi*, the syndrome is not confined to a sting by this species alone.

4.2.1. Distribution

Irukandji syndrome occurs from Exmouth in Western Australia, across northern Australia and down the Queensland coast as far south as the coast to the west of Childers (Williamson et al., 1996). *Carukia barnesi* has been morphologically identified as far south as Mackay (Fenner, 2004).

4.2.2. Description and habits

This creature is minute compared with other dangerous jellyfish (Fig. 1). Its squarish bell is barely 12 mm wide and its 4 tentacles vary in length from a few centimetres to 35 cm (Williamson et al., 1996). Clumps of nematocysts (mammilations) are seen as tiny red dots over the bell, where they are in tightly packed 'collars,' as well as in ring formations on the tentacles. The body and tentacles are almost completely transparent in water. The second of the 2 original specimens collected by Barnes was only captured because his attention was drawn to the peculiar movements of a small fish captured by a tentacle (Barnes, 1965b).

Very little is known about the habits of *Carybdea barnesi*. It appears in shallow coastal and in deep water outside the Greater Barrier Reef in the summer months and, may come close to the shore when the seas are quite rough. A full description of this creature has been published by Southcott (1956) who named it after Barnes. He compounded the generic name *Carukia* from *Carybdea* and Irukandji.

Morphologic differentiation of *Carukia barnesi* and *Carybdea rastoni* may be difficult—both are small carybdeids with a box-shaped bell and 4 tentacles. Moreover, numerous other small carybdeids exist which are less well described. Compared

with *Carukia barnesi* however, the bell of *Carybdea rastoni* is somewhat squatter, a little larger and more cuboid, it has pink gonads, a 'hook' in the pedalial canal and, obvious gastric cirri in the corners of the stomach (Williamson et al., 1996). *Carukia barnesi* is confined to tropical waters and it has systemic as well as local effects.

4.2.3. Venom

The venom appears to contain a potent neuronal sodium channel modulator as indicated by in vitro experiments and induces high levels of catecholamines in vivo with resultant tachycardia, increased cardiac output and systemic and pulmonary hypertension (Winkel et al., 2005). The hyperadrenergic state may explain in part the clinical features of the Irukandji syndrome.

4.2.4. Envenomation, the 'Irukandji syndrome'

4.2.4.1. Local effects. The victim rarely sees the offending jellyfish but is often, but not always, aware of a sting, usually slight, to the upper body while swimming in deep water. Sometimes the sting is unnoticed and it is the onset of symptoms which forces the victim to leave the water. There is no banding or puncture mark, just an oval area of barely perceptible erythema measuring 5×7 cm, which is much larger than the area of contact with the bell (Barnes, 1964). Irregularly spaced papules ('goose pimples') up to 2 mm in diameter develop within 20 min of the sting and then fade but the erythema my last several days (Fenner and Carney, 1999).

4.2.4.2. General effects. From 5 min to as late as 2 h after the sting, but usually after about 30 min or so, marked general symptoms may develop. Severe low back pain, cramping muscle pains, nausea, vomiting, profuse sweating, headache, restlessness and agitation almost invariably occur and sometimes with hypertension. Abdominal pain is associated with spasm of the muscles of the abdominal wall and cramps occur in the muscles of the limbs. Full recovery occurs after 1 or 2 days of nausea, pain and prostration. Barnes (1964) stated that:

> Of the 60 documented cases of Irukandji stinging, 55 patients presented with abdominal pain, 35 complained of limb pains, 34 were reported to have cough, nausea or vomiting, and 24 had severe backache. Neuralgias and joint pains were troublesome symptoms in all four patients observed in hospital overnight, and doubtless the incidence would have been higher had more patients remained under observation. (Irukandji victims are usually treated as outpatients, and discharged when presenting symptoms abate. Unnecessary suffering and anxiety result from this practice.).
>
> Tingling, shivering, weakness, cramps, headache, dry mouth and itch were recorded infrequently. Here again the true incidence may well have been higher, for these are second-rank symptoms, likely to be disclosed only in response to specific inquiry. The one effect usually ignored by victims, but figuring prominently in medical records, was profuse sweating.

In this paper, Barnes also described in detail the effects when the first captured specimens of *Carukia barnesi* were applied to the arms of himself, his son and a lifesaver. The illnesses they suffered incorporated all the described features of the mysterious 'type A' stings.

In a later study of 62 victims presenting in Cairns during 1996 (Little and Mulcahy, 1998), the symptoms and signs were abdominal cramps (40 per cent), hypertension (50 per cent), back pain (39 per cent), nausea and vomiting (39 per cent), limb cramps (34 per cent), chest tightness (26 per cent) and marked distress (24 per cent).

On one occasion the syndrome was associated with loss of consciousness which was attributed to cerebral oedema (Fenner and Heazlewood, 1997).

4.2.4.3. Acute cardiac failure. Cardiogenic pulmonary oedema has also been described in individual case reports (Herceg, 1987; Fenner et al., 1988; Martin and Audley, 1990; Little et al., 2001). It occurred in 2 of 62 victims (Little and Mulcahy, 1998), In a retrospective review of 12 serious cases (Little et al., 2003), pulmonary oedema was a constant feature. The initial phase of envenomation was mild skin pain followed at 30 min by considerable muscle pain and cramps with associated tachycardia and hypertension. After a mean of 14 h post sting (range 1.5–18 h), pulmonary oedema was evident radiologically and in some cases was associated with hypokinetic cardiac function, reduced cardiac output and raised cardiac enzymes. Required treatment was oxygen therapy, diuretics, vasodilators, inotropic support and mechanical ventilation or application of CPAP. Of note is the fact that in none of the 'mild' cases was a positive

identification made of a creature causing the envenomation although in one (Little et al., 2001) a tentacle (macerated) appeared to belong to an as yet unnamed carybdeid jellyfish (Little and Seymour, 2003).

In a retrospective study (Huynh et al., 2003) of 116 patients presenting to Cairns Base hospital with Irukandji syndrome over a 12-month period 2001/2002, 39 of 50 who had skin scrapings performed had *Carukia barnesi* nematocysts identified from skin scrapings. One patient who died had an unidentified cnidome in skin scraping. In a prospective study of victims of jellyfish stings presenting to the Royal Darwin Hospital (O'Reilly et al., 2001), 4 of 40 patients had Irukandji syndrome but identifying nematocysts could not be identified in sticky-tape sampling of sting site in any of them.

Thus, although it is now certain that *Carukia barnesi* can cause the Irukandji syndrome, other species may be responsible for the most severe form of an illness which includes cardiac failure.

The mechanism of cardiac failure is speculative but appears to be secondary to hypertension or direct myocardial depression. It seems unlikely that the relatively brief period of hypertension, and in some cases its mediocrity before the onset of cardiac failure, is the sole cause.

Fenner et al. (1986a) speculated that the mechanism of hypertension may be caused by catecholamine release. Although this has been demonstrated in an animal model of *Carukia barnesi* envenomation (Winkel et al., 2005) it has yet to be confirmed in human cases. Antihypertensive therapy may be required in the initial phase of management. Infusions of phentolamine have been used successively for this purpose but a 'titratable' nitrate would be preferred. Fenner and Lewin (2003) proposed instigating pre-hospital treatment of hypertension with sublingual nitrates.

4.2.5. *Differential diagnosis*

In 1964, Barnes observed that stinging capsules had not been recovered from *Carukia barnesi* stings, and suggested that negative skin scrapings indirectly assist differentiation from other jellyfish stings and that the diagnosis is usually clear cut on clinical grounds. Greater success has been achieved in more recent times (see above, Huynh et al., 2003). Importantly, Barnes (1964) makes the point that the condition can be simulated by gastric poisoning, and by various surgical emergencies such as peptic ulcer, ruptured spleen, ruptured ectopic pregnancy and acute appendicitis. Myocardial infarction and decompression sickness are also alternative diagnoses (Fenner and Carney, 1999).

Barnes predicted that the 'Irukandji' syndrome would prove to be caused by a variety of species of jellyfish. In so far as the effects of muscle pain are concerned this has been observed for species of *Tamoya*, *Physalia* and *Carybdea* and other genera both in and outside Australian waters (Williamson et al., 1996; Yoshimoto and Yanagihara, 2002). Although several detailed case reports are available (Fenner et al., 1986a, b, 1988; Herceg, 1987; Martin and Audley, 1990; Hadok, 1997; Cheng et al., 1999; Little et al., 2001) on only one occasion was the victim able to offer a description of an offending jellyfish. This was a 28-year-old diver who experienced a typical Irukandji syndrome after contact with a small box-shaped jellyfish with 4 tentacles with an overall size of a thumb. His sketch of the animal closely resembled *Carukia barnesi* (Hadok, 1997). After another instance (Fenner et al., 1988) 2 specimens of *Carukia barnesi* were captured in the same vicinity and under the same conditions where a severe envenomation had occurred 3 days previously. Although these latter accounts are highly suggestive that *Carukia barnesi* is one species responsible for Irukandji syndrome, they are not conclusive.

Irukandji syndrome is not confined to Australian waters. It has been reported from Papua New Guinea, Hawaii, Japan and China (Williamson et al., 1996) and an 'Irukandji-like' syndrome recently from southern USA. Grady and Burnett (2003) reported 3 mild-moderate 'Irukandji-like' cases off Key West, Florida and speculated that a Carybdeid may have been responsible. In none of the cases was a jellyfish observed. Similarly, mild stings from unidentified jellyfish in Thailand and in the Gulf Sea (Qatar) were deemed responsible for acute myocardial infarction in a swimmer and in a diver free of ishaemic heart disease (de Pender et al., 2006; Salam et al., 2003).

4.2.6. *First-aid*

Although domestic vinegar has been shown to inactivate undischarged nematocysts of *C. fleckeri* (Hartwick et al., 1980), *Carybdea rastoni* (Fenner and Williamson, 1987) and *Tamoya* sp. (Fenner et al., 1985), this has not been decisively demonstrated for *Carukia barnesi*. Fenner et al. (1988) reported that vinegar inhibited discharge of nematocysts from a small carybeid captured where a case

of Irukandji syndrome had occurred 3 days previously. That jellyfish resembled *Carukia barnesi* but was not positively identified. Nonetheless, Williamson et al. (1996) recommend the use of vinegar for the syndrome.

4.2.7. Clinical management and prognosis of envenomation

Pain relief is the most important feature of management in mild-moderate cases. Repeated doses of IV or IM opiates may be required. Barnes (1964) recommends pethidine initially by the intravenous route but fentanyl is probably better in serious cases because of less propensity to cause hypotension.

Most cases of stings in the Cairns area are mild (Little and Mulcahy, 1998; Huynh et al., 2003) but 2 fatalities have been attributed to unseen jellyfish causing the Irukandji syndrome further south and on the Great Barrier Reef (Fenner and Hadok, 2002; Huynh et al., 2003). In these fatalities, intracerebral haemorrhage was associated with severe hypertension. One of these occurred off Hamilton Island in the Whitsunday Islands (20°20′ S, 148°56′ E) and the other some 1300 km north on the Great Barrier Reef off Port Douglas.

In severe cases in which pulmonary oedema and cardiac failure are present, admission to an intensive care unit is needed. Mechanical ventilation or CPAP and 'titratable' inotropic and vasodilator therapy may be required. *C. fleckeri* antivenom is ineffective (Fenner et al., 1986b).

Interestingly, although *C. fleckeri* antivenom binds to this crude venom preparation in vitro (Wiltshire et al., 2000) it is clinically ineffective in treatment of the Irukandji syndrome (Fenner et al., 1986b) and it did not prevent tachycardia and vessel contraction during Irukandji venom provocation in vitro (Winkel et al., 2005).

Corkeron (2003) used intravenous magnesium sulphate (10 mmol loading dose plus an infusion of 5 mmol/h for 20 h) to immediately ameliorate pain and hyperadrenergic features (hypertension, agitation, diaphoresis, piloerection and dysnoea) of Irukandji syndrome in a previously well 26-year-old man who had been stung by an unknown jellyfish. The basis of the decision to use magnesium was its ability to decrease vascular resistance in hyperadrenergic states and its suppression of catecholamine release. The analgesic effect however remains unexplained. Of additional interest was a high tropinin I level (6.4 mcg/L) associated with only a moderate level of hypertension (170/100 mmHg) and normal echocardiographic function. In a further series of 10 victims with Irukandji syndrome, intravenous magnesium salts provided pain relief, as assessed by serial pain scores before and after treatment, and a reduction in blood pressure (Corkeron et al., 2004).

4.3. Morbakka

This jellyfish is also called the 'Moreton Bay Stinger' or the 'Fire Jelly.' It is a relatively large carybdeid cubozoan (Fig. 2) found from Port Douglas in north Queensland to Moreton Bay in the south. Although it closely resembles *Tamoya virulenta* (Williamson et al., 1996) it has not yet been formally identified. Until such time, Southcott (1985) proposed the name 'Morbakka'—derived from 'Moreton bay carybdeid medusa.' Characteristically, the transparent bell is deeper than it is wide with measurements of a large specimen 18 and 12 cm, respectively (Fenner et al., 1985). The 4 tapered tentacles are mauve in colour and extend to 60 cm.

Stings do not have the same dire consequences as those from other smaller carybdeids *Carukia barnesi* ('Irukandji') or *Carybdea rastoni* ('The Jimble'). A sting raises a white wheal approximately 10 mm wide and surrounded by a red flare resembling a superficial burn. It is associated with severe burning pain of almost immediate onset and lasting 24 h (Fenner et al., 1985). The appearance of the lesion and the sensation give rise to the common name 'Fire Jelly.' However, there may also be associated respiratory distress and throbbing lumbar pain (Williamson et al., 1996) reminiscent of 'Irukandji' syndrome. The lesions may show a characteristic tapering corresponding to the tentacle and may show 'ladder' markings similar to a chirodropid sting. The lesions may vesiculate and become pruritic. Skin necrosis may occur. The surface of the bell has nematocysts arranged in clusters (warts) which may cause multiple punctate lesions within an area of erythema (Williamson et al., 1996). Typical undischarged and discharged nematocysts may be obtained from skin scrapings. Undischarged nematocysts are inactivated by vinegar (Fenner et al., 1985).

4.4. Darwin carybdeid

This is a small four-tentacled carybdeid has a transparent bell of approximately 3 cm in diameter with white mammilations and a single tentacle

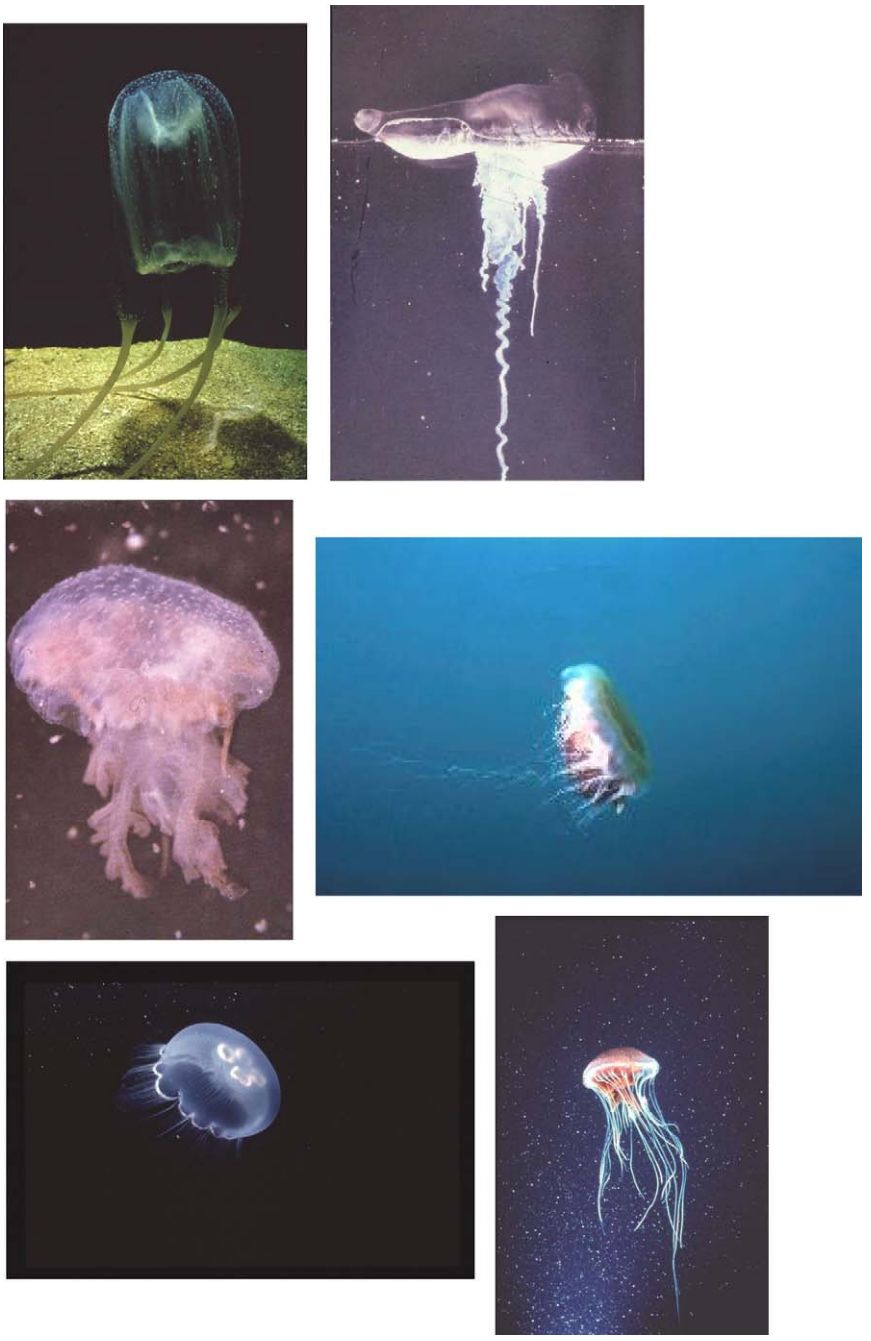

Fig. 2. Top panel: (left) Morbakka (photo Ben Cropp); (right) Bluebottle (*Physalia utriculus*) (photo K Gillett). Middle panel: (left) Little Mauve Stinger (*Pelagia noctiluca*) (photo N Coleman); (right) Hair jelly (*Cyanea capillata*) (photo Mary Malloy). Bottom panel: (left) Moon jellyfish (*Aurelia aurita*) (photo Karen Gowlett-Holmes); (right) Sea nettle (*Chrysaora* sp.) (photo Karen Gowlett-Holmes).

arising from each pedalium. It morphologically resembles the Morbakka but is considerably smaller. The first 2 cases of envenomation, accompanied by the newly-discovered captured jellyfish in Darwin, were reported by Williamson et al. (1996). A further 6 cases in Darwin were identified by O'Reilly et al. (2001) by nematocyst identification. The original envenomation syndrome was described as one of moderate pain at the site of sting which was responsive to local application of ice-water and

without systemic symptoms (Williamson et al., 1996) although the more recent description included abdominal pain (O'Reilly et al., 2001).

5. 'Portuguese Man-O'-War' *Physalia physalis;* 'bluebottle' *physalia utriculus*

Although *Physalia* spp. are not true jellyfish but colonies of siphonophores (class Hydrozoa) they are commonly regarded as a jellyfish and are the most frequent cause of significant stings in Australia, estimated at 10,000 per annum on the eastern coast (Fenner and Williamson, 1996). Currently, it is uncertain whether *Physalia* exists as 2 or more separate species. Fenner et al. (1993) argue for resurrection of a former differentiation into 2 species on the basis that one has several main tentacles (*Physalia physalis*) and can cause major systemic symptoms; while the other has only one main tentacle (*Physalia utriculus*) and does not cause severe symptoms.

Although no definite fatalities have been attributed to *Physalia* in Australia, it can cause severe local pain and, if present in swarms (armadas), may warrant closure of beaches to swimmers. Three deaths have been attributed to the Atlantic *Physalia physalis* on the south east coast of the United States.

5.1. Distribution

Species of *Physalia* are found in all hot and temperate waters of the world. Both the single tentacled and the small multi-tentacled specimens may be found in Australian waters.

5.2. Description and habits

Each *Physalia* is a siphonophore colony of hydrozoans in 4 groups, each with a specific role. One group forms a gas-filled float keeping the colony on the surface and enabling wind-assisted travel (the 'sail'). In *Physalia physalis*, the multi-tentacled species, the float measures from 2–25 cm in length while in *Physalia utriculus* it is smaller but up to 10 cm in length (Fig. 2). Another group of animals involves reproduction. Another has polyps and tentacles with nematocysts, acting as a 'keel' or 'sea anchor' and is responsible for the collection of food while a fourth group performs digestion. The jellyfish remains permanently on the surface of the sea. *Physalia* colonies, or groups consist of specimens with 2 mirror images, which rely on movement by sailing either to the left or to the right at 45° to the wind. Southcott (1968) described the 'sailing habits', as well as many other aspects of this creature. Parts of the float and all the tentacles are usually a bright blue colour but may have a purplish colour in specimens from the Atlantic. The long fishing tentacle of a large (25 cm) multi-tentacled species is reputed to be up to 30 m long while that of a single-tentacled species is 2–3 m (Williamson et al., 1996). Being a surface creature, *Physalia* presents a significant hazard to swimmers particularly when the creatures gather in large numbers. *Physalia* stranded on a beach may also cause stings if handled, even after several days of dehydration.

5.3. Venom apparatus

When the main tentacle contracts, nematocysts become arranged in 'stinging buttons' (Southcott, 1968) which upon contact may produce a lesion, usually linear, like a row of beans or buttons, while uncontracted tentacles may give fine linear stings. Undischarged nematocysts are spherical (Fig. 1).

5.4. Venom

Lane (1960) extracted toxin from homogenised *Physalia physalis* nematocysts and found it to be a complex mixture of labile proteins. The certain lethal dose by the intraperitoneal route in 30 g Swiss mice was 2.0–2.5 mg/kg. The mice showed an initial hyperactivity and tremors, but then developed a progressive flaccid paralysis and died within 1–48 h, depending upon the dose administered.

Burnett and Calton (1974) isolated some 9 mouse lethal factors from *Physalia physalis* nematocyst suspension and determined their molecular weights to be approximately 150 kDa. Tamkun and Hessinger (1981) have purified physalitoxin from isolated *Physalia physalis* nematocysts and have found it to be responsible for the crude toxin's experimental haemolytic and lethal effects. The intravenous LD_{50} in 18–20 g mice was 200 μg/kg for the crude toxin and 145 μg/kg for physalitoxin. Physalitoxin is a glycoprotein containing 10.6 per cent carbohydrate and is rod-like in shape with an estimated molecular weight of 240,000 and a sedimentation coefficient of 7.8. This latter finding is compatible with the earlier molecular weight estimate of Burnett and Calton. A high molecular weight toxin (P3) from *Physalia physalis* was

observed to reversibly block glutamate receptors (Mas et al., 1989).

In vitro studies showed that *Physalia physalis* venom caused exocytosis of mast cell granules and their eventual cell lysis which suggested the release of histamine (Cormier, 1984). The venom caused vasodilatation in skeletal muscle vascular beds of anaesthetised dogs (Loredo et al., 1985) and in isolated rabbit arterial ring segments (Loredo et al., 1986). Venom obtained from the smaller of 2 nematocyst organelles types, separated by flow cytometry, was lethal to chick embryonic cardiocytes (Burnett et al., 1986).

Lane (1967) showed the intravenous toxin produced marked conduction disturbances in the hearts of rats. He also found the toxin was a potent stimulator of smooth muscle. The cardiovascular systems of the rat and dog were affected adversely by venom (Larson and Lane, 1966; Hastings et al., 1967). The mechanism of action was suggested to be depolarisation by inhibition of the Na^+/K^+ -ATPase activity (Larson and Lane, 1966). Positive inotropy in isolated rabbit atria proportional to the extracellular calcium level was observed by Bonlie et al. (1988). Burnett et al. (1985) observed that the calcium channel blocker, verapamil, delayed death in envenomated animals and suggested it may be a therapy for envenomation. However, although venom increases calcium influx into chick heart cells, the action is unaffected by a range of L-type calcium channel blockers, and by a T-type calcium channel blocker but is inhibited by certain trivalent and divalent transitional metals (Edwards et al., 2000) which are known to block calcium channels. These investigators also observed that sodium influx, also increased by venom, was not blocked by flecainide, a sodium channel blocker, and suggested that the venom acts by activating or forming non-selective channels or pores in membranes (Edwards et al., 2000). Later studies (Edwards and Hessinger, 2000) showed that the venom caused release of cytoplasmic lactate dehyrogenase at the same dose which caused influx of calcium thus suggesting the venom acts by 'permeabilizing' the plasma membranes of cells. These effects were observed not only with embryonic chick heart cells but also with rat pituitary cells, foetal rat lung cells and fibroblasts. The effects were not blocked by ouabain (which blocks Na^+/K^+-ATPases) or by vanadate (an ATPase inhibitor) but were blocked by Zn^{2+}. The transitional metal lanthanum blocked Ca^{2+} influx but not the cytolytic activity of the venom.

5.5. Envenomation

Sharp pain is instantaneous and red lines with scattered papules rapidly develop. The pain may soon become 'a violent aching pain' (McNeill and Pope, 1943). The severity and appearance of local effects are in proportion to the size of the tentacle and its state of contraction. Classically, the wound will resemble a linear 'string of beans' consisting of discrete oval weals, which are blanched centrally and surrounded by erythema. In severe cases vesicles may develop, but in most cases signs of the injury have faded within 24 h. Local pain may last some 2 h and may spread through the whole limb, or around the trunk when body stings have occurred. Movement of the injured limb may increase the severity of the pain. Significant general signs are uncommon, but headache, vomiting, abdominal pain and collapse may occur.

5.6. Differential diagnosis

Physalia is well known and the offending creature is usually clearly visible. The characteristic injury produced usually allows distinction from other jellyfish stings. Skin scrapings may demonstrate the characteristic spherical nematocysts.

5.7. First-aid

Vinegar is useful as a first-aid treatment of some jellyfish stings, but its use for *Physalia* stings is controversial. Although the application of vinegar was concluded to reduce the pain of Australian *Physalia* stings (Turner et al., 1980) and inhibited nematocyst discharge from *Physalia physalis* tentacles (Burnett et al., 1983), it was later observed to cause discharge of nematocysts of the Australian multi-tentacled species at a grade of 2 on a scale of 5, while methylated spirits caused discharge to grade 5, in contrast to water which caused no discharge (Exton, 1988; Fenner et al., 1993). As it would be difficult to discern between single-tentacled and multi-tentacled species, vinegar cannot be recommended as a first-aid treatment for any *Physalia* stings, nor should methylated spirits be used. Adherent tentacles should be picked off. Exton et al. (1989) observed that pain relief was best obtained by the application of cold packs or ice but

in a randomised trial 53% of victims of stings obtained relief after 10 min of hot water immersion (45 °C) versus 32 per cent of victims treated with application of cold packs ($p = 0.039$), and a greater difference (87 per cent vs. 33 per cent) was observed at 20 min (Loten et al., 2006).

5.8. Clinical management and prognosis of envenomation

Persistent pain usually responds to the application of a local anaesthetic ointment, such as lignocaine 5 per cent (Edmonds, 1975). Most stings are quite minor in nature, but they do pose a significant public health problem from time to time. There is no specific antivenom and *C. fleckeri* antivenom was ineffective against experimental lethal and dermatonecrotic properties (Baxter and Marr, 1974).

Several deaths have been reported after envenomations by the Atlantic *Physalia physalis* (Burnett and Gable, 1989; Stein et al., 1989). One case involved a scuba diver who was wearing the bottom half of a wetsuit with shoulder straps. He apparently contacted tentacles while surfacing off-shore near Jacksonville, North Carolina, USA. He called for help but was found pulseless and apnoeic by rescue swimmers who reached him after 2–3 min. Resuscitative efforts were unsuccessful. A *Physalia* float and numerous tentacles were observed attached to his arms and wetsuit. Serum obtained at autopsy did not show any immune species-specific *Physalia* or *Chrysaora* (sea nettle) antibodies. Another probable case was a swimmer at Miami Beach, Florida. He staggered from the water with *Physalia* tentacles on his chest, arms and legs. He collapsed and died on the beach despite expired air resuscitation. A third case was a woman who emerged from the sea near Palm Beach Florida with the float and tentacles wrapped around her arms. She was in extreme pain and within minutes became dyspnoeic and comatose. An initial ECG showed normal sinus rhythm with a rate of 80/min but she was apnoeic and within another 2 min she became bradycardic. CPR was commenced immediately and endotracheal intubation accomplished within 7 min of the sting. Despite administration of atropine and adrenaline she was pulseless, without a recordable blood pressure, in asystole and had fixed dilated pupils. Although sinus rhythm was restored after an hour of continuous CPR she died after 5 days of ventilator support without regaining consciousness. The cutaneous linear lesions were 1–2 mm in width and were estimated to be 2.75–3.50 m in length. Numerous elongated and oval discharged nematocysts were identified on the skin and nematocyst threads protruded from the epidermis. No myocardial damage was detected although there elevated CPK levels. Death was attributed primarily to respiratory arrest.

Gollan (1968) described how a young man in Western Australia collapsed some 15 min after a sting attributed to *Physalia*. His breathing stopped, heart sounds could not be detected, and his pupils were dilated and unreactive to light. Fortunately, he responded dramatically to an intravenous injection of antihistamine and soon recovered. There may have been allergic basis to this severe reaction, because some 12 years before the patient had developed facial swelling, when swimming in a presumedly tidal river. Burnett et al. (1986) accumulated clinical and laboratory evidence of the development of hypersensitivity to the *Physalia* as well as to other jellyfish.

An unusual case of brachial artery spasm which followed a probable second contact with *Physalia* was reported by Adiga (1984). Intra-arterial injection of reserpine relieved the spasm and a proposed sympathectomy was avoided. Acute vascular insufficiency has occurred after other stings by unidentified jellyfish outside Australia (Williamson et al., 1988).

Eye injuries have also been attributed to *Physalia* in Australia (Hercus, 1944).

6. The Little Mauve Stinger, *Pelagia noctiluca*

Pelagia noctiluca as its name implies is an open water (pelagic) species which has a nocturnal phosphorescent bell measuring from 3 to 12 cm in diameter in mature specimens. The edge of the bell is scalloped into 16 lappets. There are 8 tentacles arising from the bell edge. It is generally coloured pink, mauve or light brown (Fig. 2). The upper surface of the bell and the 4-frilled mouth parts are studded with collections (warts) of nematocysts.

6.1. Distribution

Pelagia noctiluca has a wide distribution in the oceans of the world, being found in tropical zones as well as colder areas, such as the north Atlantic and north Pacific.

6.2. Venom

Little is known about the venom except that it is cytotoxic (Mariottini et al., 2002) and its calcium dependant activation of nematocysts is blocked by treatment with gadolinium (Salleo et al., 1994). The venom is antigenic. A case of anaphylaxis after possible contact with *Pelagia noctiluca* has been recorded (Togias et al., 1985) as well a case of Guillain-Barré syndrome (Pang and Schwartz, 1993). Reactivity with *Chrysaora quinquecirrha* and *Physalia physalis* monoclonal antibodies has been observed (Olson et al., 1985).

6.3. Envenomation

This species has not caused human fatalities, but has proved to be a nuisance when it has appeared in huge numbers in Australia during major surfing championships. Its tentacles or bell can cause local pain and, on one occasion, swimmers in a race near Brisbane who made contact with it 'collapsed' (Bloomfield, 1959).

Williamson (1981) reported that the pain is immediate and may be distressing, and that irregularly shaped weals resembling urticaria may develop. He also described the occurrence of dyspnoea after massive stingings. Recurrent skin eruptions may occur without repeated contact with the jellyfish (Mansson et al., 1985). A lesion developed hyperpigmentation but responded to topical hydroquinone (Kokelj and Burnett, 1990).

It is well known in Mediterranean (Queruel et al., 2000) and Adriatic seas. An epidemic of stings in the Adriatic due to *Pelagia noctiluca* was described by Maretic et al. (1980). Along the coasts of Yugoslavia in 1978 an estimated 250,000 people were stung. No serious injuries were reported, but in some cases the initial intense pruritus did not subside for a week. Trawlers and fishing boats had problems during this epidemic as the jellyfish fouled their screws and fishing gear, as well as filling their nets.

6.4. First-aid

Work by Fenner and Fitzpatrick (1986) suggest this is one of several jellyfish whose nematocysts may be triggered by vinegar. Instead, iced water or ice–water mixtures should be applied. The stings are not considered to endanger life.

7. The Hair Jelly, *Cyanea capillata*

This jellyfish is also called the 'Sea Blubber,' the 'Hairy Stinger' or 'Snottie.' There are a number of species in the genus *Cyanea* and some others also have highly descriptive common names, for example, 'Hairy Stinger,' 'Sea Nettle,' 'Hairy Jelly' and 'Lion's Mane.' Barnes (1960) described one as 'a repulsive big slimy jellyfish,' which bears a 'general resemblance to a mop hiding under a dinner-plate.'

This jellyfish has a flattened plate-like (saucer-shaped) bell, the edge of which is turned inwards and shaped into 16 lappets (Fig. 2). It may be more than 1 m across in Australian waters, but in the cold Antarctic waters its size may be greater. It is a semi-transparent white, light yellow or brown. From beneath the central part of the bell arise the 4 mouth arms which secretes a thick mucus—hence a common name 'Snottie.' These mingle with a mass of numerous tentacles, more than 1000, which arise more peripherally as 8 V-shaped clusters. The tentacles, delicate and hairy, may trail many metres and detach easily but when free are still capable of inflicting a painful sting.

7.1. Distribution

Cyanea has a widespread distribution and is found in all Australian coastal waters.

7.2. Venom

Rice and Powell (1972) isolated a single toxic protein from nematocysts taken from specimens of *Cyanea capillata* collected in Chesapeake Bay in the United States. The intraperitoneal LD_{50} in mice (weight unspecified) was 6 mg/kg. These workers could not produce significant self-inflicted stings with these specimens, which is in contrast to the Australian clinical and experimental experience. Walker et al. (1977) extended earlier findings concerning the lethal cardiotoxic effects of the toxin in experimental animals by tissue culture studies. The toxin was found to directly disturb enzymes involved in ion transport. Walker (1977) determined the intravenous LD_{50} in mice (weight unspecified) to be 0.3 mg/kg and he estimated the main toxin, which was a basic protein, to have a molecular weight of approximately 70 kDa.

7.3. Envenomation

No deaths have been attributed to this creature. Barnes (1960) considered *Cyanea* to be a significant cause of stings in which formation of weals was a major manifestation. Contact with the tentacles may produce a burning feeling that develops into a severe pain. Barnes states that a fine, stippled, linear weal bordered by a narrow flare may develop. Williamson et al. (1996) illustrate the weal as having a characteristic saw tooth pattern. The pain and swelling subside after 15 min or so, leaving a bright red streak which may persist for several days and was considered by Barnes to a valuable diagnostic aid. Shortly after the stinging, nausea and abdominal pains may develop. At times, profuse sweating, muscle cramp and respiratory distress are seen.

In Europe, last century stings from this jellyfish were used to treat various nervous diseases. However, because of complications such as glottic oedema, the therapy was soon abandoned (Cleland and Southcott, 1965). The occurrence of glottic oedema may have been an allergic reaction. As with other jellyfish, injuries to the eye have occurred after contact with the tentacles or nematocysts shed by members of this genus (Mitchell, 1962; Winkel et al., 2002b).

7.4. First-aid

Vinegar should not be poured over the lesion or any adhering tentacles since it causes discharge of nematocysts (Fenner and Fitzpatrick, 1986). Cold packs relieve the pain (Exton et al., 1989).

8. Saucer Jelly or Moon Jellyfish, *Aurelia aurita*

Aurelia species have a worldwide distribution. *A. aurita* is characterised by a smooth flattened saucer-like bell of diameter up to 30 cm and whose edge is slightly scalloped into 8 lappets. It is coloured blue-white. The numerous tentacles are very short and appear as a fringe from the edge of the bell (Fig. 2). The 4 oral arms are thick and prominent.

Although there are many stings it was regarded by Cleland and Southcott (1965) as relatively harmless or even non-stinging, but Burnett et al. (1988) described a case of significant envenomation occurring in the Gulf of Mexico. A swimmer sustained large stings to an arm and knee. Instant pain was followed within a few minutes by urticaria, then by ulceration which encrusted 3–9 days later. The initial pain disappeared within 30 min but was followed by regional pain after $4\frac{1}{2}$ days which lasted for 24 h. Post-inflammatory hyperpigmentation was still visible at the sites after 2 weeks. Immunospecific antibodies against *Aurelia* antigens were detected which also cross-reacted with antigen derived from *Chrysaora quinquecirrha* (North American Sea Nettle).

A nematocyst preparation of venom derived from specimens from the Red Sea and from Chesapeake Bay had lethal, dermatonecrotic, vasopermeability and haemolytic properties in mice (Radwan et al., 2001).

9. Sea nettle, *Chrysaora* sp.

Species of *Chrysaora* are widely distributed in Atlantic, Pacific and Indian oceans where 'Sea nettle' is a common name (Fig. 2). An unnamed species in South Australian waters (Cleland and Southcott, 1965) has a multi-scalloped saucer-shaped bell about 6 cm in diameter and about 40 or more tentacles. The upper surface of the bell has a dense pattern of brown spots which thin to form radial streaks towards the bell edge. The 3 mouth arms are also studded with brown spots. Contact with tentacles causes minor to moderate stinging followed by appearance of multiple punctate weals and then pink macules which coalesce. The rash may last a month. A severely stinging species of *Chrysaora* is also present in Western Australian waters (Williamson et al., 1996).

10. Other jellyfish

There are many other species of jellyfish which can cause painful stings to humans in Australian waters. Some stings occurring on the Great Barrier Reef are probably due to unrecognised species. The most comprehensive reference texts on significant Australian jellyfish are Cleland and Southcott (1965) and Williamson et al. (1996). These include the following.

Catostylus mosaicus ('*Blubber Jellyfish*'): This species has a mushroom-shaped bell up to 35 cm diameter with cruciate markings visible in the bell when viewed from above. It has no tentacles but the nematocysts are borne on 8 long stout carrot-shaped mouth arms. It is very common in south-east Australian waters. A venom extract had mouse haemolytic, oedema and haemorrhage-inducing activities (Azila et al., 1991).

Pseudorhiza haeckeli: This species has a mushroom-shaped smooth-edged bell up to 25–30 cm in diameter. There are no tentacles and three clumped wide frill-edged mouth arms. It gives a mild sting lasting up to 30 min.

Olindias singularis: This is a small jellyfish with a clear mushroom-shaped bell 15–20 mm in diameter and multiple brown 2.5–15 cm long tentacles trailing from the edge of the bell. It gives a mild sting and leaves a linear 3–4 mm wide wheal lasting about 30 min.

Cassiopea sp. '*Upside down Jellyfish*': This has a greenish-grey blue bell like a flat saucer of diameter up to 40 cm. The bell has a distinctive central concavity in the outer surface. The edge of the bell is finely scalloped with many small lappets in groups of five. There are 4 pairs of branched mouth arms from which arise short tentacles. It lies on the bottom of the ocean with arms directed upward collecting descending food. Its sting is mild. A nematocyst preparation of venom derived from 2 species had lethal, dermatonecrotic, vasopermeability and haemolytic properties in mice (Radwan et al., 2001; Torres et al., 2001)

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