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## ABSTRACT

Ciguatera poisoning is a food-borne neuro-intoxication caused by consumption of finfish that have accumulated ciguatoxins in their tissues. Ciguatera is a distressing and sometimes disabling condition that presents with a self-limiting though occasionally severe gastro-intestinal illness, progressing to a suite of aberrant sensory symptoms. Recovery can take from days to years; second and subsequent attacks may manifest in a more severe illness. Ciguatera remains largely a pan-tropical disease, although tourism and export fish markets facilitate increased presentation in temperate latitudes. While ciguatera poisoning in the South Pacific was recognised and eloquently described by seafarers in the 18th Century, it remains a public-health challenge in the 21st Century because there is neither a confirmatory diagnostic test nor a reliable, low-cost screening method to ascertain the safety of suspect fish prior to consumption. A specific antidote is not available, so treatment is largely supportive. The most promising pharmacotherapy of recent decades, intravenous mannitol, has experienced a relative decline in acceptance after a randomized, double-blind trial failed to confirm its efficacy. Some questions remain unanswered, however, and the use of mannitol for the treatment of acute ciguatera poisoning arguably deserves revisiting. The immunotoxicology of ciguatera is poorly understood, and some aspects of the epidemiology and symptomatology of ciguatera warrant further enquiry.

## BACKGROUND

Ciguatera fish poisoning (CFP) is an ichthyotoxaemia caused by eating tissues of fish that are contaminated by potent neurotoxins known as ciguatoxins. The ciguatoxins are a family of cyclic polyether compounds with molecular weights in excess of 1 kDa. Figure 1 shows the structure of Pacific ciguatoxin 1 (P-CTX-1), which is the most toxic of the known congeners. The ciguatoxins are lipophilic, stable under mildly acidic and basic conditions, and heat-stable (and therefore not destroyed by cooking).

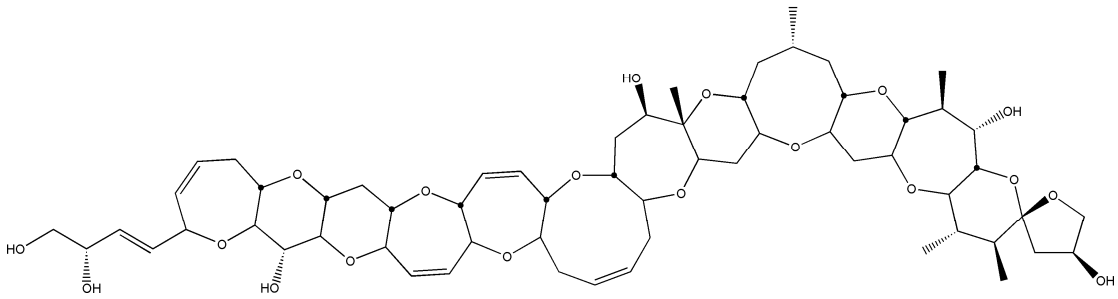


**FIGURE 1.** The molecular structure of Pacific ciguatoxin-1 (P-CTX-1)

Ciguatoxins originate from dinoflagellates, a phylum of unicellular eukaryotic microalgae. Epiphytic dinoflagellates, principally in the genus *Gambierdiscus*, produce precursor ciguatoxins that typically undergo biotransformation as they are transferred up through several trophic levels. Herbivorous fish, and in some cases molluscs and crustacea, graze on macroalgae on which toxic dinoflagellates are present, thus becoming primary vectors for ciguatera toxins. As first-order consumers are predated by carnivorous fish, precursor ciguatoxins become more oxidised, more polar (although remaining highly lipophilic, like the precursors) and more toxic. Thus the main vectors of CFP to humans are carnivorous fish, although some herbivorous fish can carry ciguatera toxins in their flesh.

Ciguatera is an environmental health problem historically associated with tropical and sub-tropical regions, although the disease is now seen in higher latitudes because of the increasing global trade in seafood products. Mass-market air travel in recent decades has also contributed to an increased incidence of ciguatera in temperate regions, as visitors can quickly return home to temperate-zone population centres after consuming ciguatoxic fish in a tropical tourist haven that also happens to be a ciguatera 'hot-spot'. Such cases may present for medical diagnosis in the acute phase of their illness. CFP is thus increasingly a global phenomenon, although its incidence remains higher in certain tropical and subtropical regions — such as many South Pacific island nations and north–eastern Australia — where ciguatoxin-carrying fish species are more likely to be caught and consumed.

There is a significant and growing body of literature on ciguatera poisoning. Many excellent and comprehensive review articles, books and chapters can be found, either presenting general overviews or focusing on specific topics such as the chemistry of ciguatoxins, symptomatology, clinical management and epidemiology, geographical distribution, food-chain dynamics, phycology, toxicology and analytical detection in biological matrices. This review includes discussion on the historical awareness of ciguatera, and the diversity of clinical and research specialties that contribute to the contemporary understanding of the disease. An overview of the clinical presentation is presented, the diagnostic curiosity of ciguatera- related acute sexual dysfunction is examined in detail, and some pharmacological interventions for ciguatera poisoning are discussed. Finally, some knowledge gaps and uncertainties are outlined, and research strategies that may advance the understanding and management of ciguatera are proposed.

## HISTORY AND CASE REPORTING

Although the term 'ciguatera' dates back to the Spanish colonisation of Cuba in the 17$^{th}$ Century, the characteristic syndrome — of gastro-intestinal, haemodynamic and neurological symptoms — was first described in the 18th Century. Earlier, incomplete references from ancient Rome and from the Tang Dynasty in China indicate awareness of the poisonous nature of fish now known to be ciguatera vectors (Russell and Egen, 1991; Pearn, 2001). Outbreaks of CFP caused significant logistic problems for the military effort in the Pacific during the Second World War, although CFP occurs in tropical and sub-tropical ocean nations across the world (Bienfang et al., 2008; Dickey, 2008). From the South Pacific, convincing descriptions of CFP were recorded in 1774 near Vanuatu by John Anderson, surgeon's mate aboard Captain Cook's Resolution; a group outbreak following a fish meal was characterised by acute gastro-intestinal symptoms, lassitude and asthenia that progressed to symptoms of aberrant temperature perception, dysaesthesias — including the sensation of teeth being loose — paraesthesias and bradycardia (Doherty, 2005). Reports of ciguatera-like illness from the early 17th Century, also arising from the Vanuatu chain, are found in the literature, with the implication that ciguatera poisoning probably predates the historical record (Lewis, 1986; Russell and Egen, 1991). The characteristic and pathognomonic signs and symptoms of CFP are now well documented in many case reports and case series, and the unusual neurological features of the disease probably help to stimulate and maintain a steady flow of case reporting and case investigation across a variety of generalist and specialist biomedical journals. Such reports can be found in the literature on tropical medicine (Hung et al., 2005; Wasay et al., 2008), clinical neurology (Achaibar et al., 2007), epidemiological surveillance (Ng and Gregory, 2000; Villareal et al., 2006), general medicine (Fenner et al., 1997; Slobbe et al., 2008), clinical toxicology (Lange et al., 1989; de Haro et al., 2003), emergency medicine (Asaeda, 2001), toxinology (Lechuga-Devéze and Sierra-Beltrán, 1995; Hamilton et al., 2009), military medicine (Arnett and Lim, 2007), gastroenterology (Sanner et al., 1997), communicable diseases (Frenette et al., 1988) and public health (Ting et al., 1998; Kipping et al., 2006). While there is a significant body of case reports in the literature, this does not suggest either that CFP is a homogeneous disease or that all facets of the illness are yet completely characterised and understood. The published case reports present some unusual

features, such as transfer of ciguatera toxins via placenta and breastmilk (Blythe and de Sylva, 1990; Senecal and Osterloh, 1991; Swift and Swift, 1991), occasional fatalities (Tonge et al., 1967; Hamilton et al., 2009), off-label pharmacotherapy (Perez et al., 2001), the increasing diagnosis of CFP in higher latitudes (due to the expanding global seafood trade and rapid movement of tourists and workers to and from ciguatera-prone geographical regions) (Asaeda, 2001; de Haro et al., 2003; Kipping et al., 2006; Slobbe et al., 2008), clinical assessment of temperature perception (Cameron and Capra, 1993) and acute sexual dysfunction and sexual transmission of CFP (Lange et al., 1989; Geller et al., 1991; Ting et al., 1998). The topic of ciguatera-related sexual dysfunction is discussed in more detail below.

## CLINICAL MANIFESTATIONS

Reviews of CFP describe an acute illness following the consumption of tropical or subtropical fish that have either a partial or frequent life-history relationship with coral reefs. Ciguatera toxins are carried by various lutjanids and epinephelids, amberjack (*Seriola* spp.), wrasse (*Chelinus* spp.) and trevally (*Caranx* spp.) as well as pelagic fish such as barracuda (*Sphyraena* spp.) and certain mackerels, particularly Spanish mackerel (*Scomberomorus commerson*). These are some of the families and genera more regularly implicated in CFP cases and outbreaks, although many other species can accumulate ciguatoxins (Lehane and Lewis, 2000).

Typically, the onset of symptoms is seen within hours of eating ciguatoxic fish. An acute and sometimes severe but self-limiting gastro-intestinal illness — with vomiting, diarrhoea and abdominal pain — is followed by a more diagnostically discrete array of neurological symptoms involving circumoral or limb-extremity paraesthesias, intense pruritus, aberrant temperature perception and dysaesthesias. Haemodynamic and autonomic signs (bradycardia, tachycardia, labile blood pressure, postural hypotension, perspiration and salivation) may be seen (Lehane and Lewis, 2000; Pearn, 2001). Non-specific acute-phase signs and symptoms, such as headache, arthralgia, myalgia, lassitude and asthenia, may supplement the diagnosis. Fever or mild hypothermia is seen occasionally (Cooper, 1964; Gatti et al., 2008; Langley et al., 2009) but most cases are afebrile (Bagnis et al., 1979; Ting and Brown, 2001; Arnett and Lim, 2007).

Reviews of clinical records document a varied and sometimes extensive array of signs and symptoms. A study of over 3000 CFP cases from the South Pacific (Bagnis et al., 1979) showed that neurological symptoms — paraesthesias of the extremities and circum-oral region, and cold allodynia — were the most frequently described symptoms (seen in >87% of cases); arthralgia and myalgia were also commonly reported (>80%), and diarrhoea was the most prevalent gastro-intestinal symptom (70%). Some differences in the frequency of specific symptoms according to ethnicity were evident (Bagnis et al., 1979). Although this observation might indicate some genetic involvement in disease progression, variables that may have influenced the ciguatoxin congener profiles to which the subjects were exposed — such as cultural preference for certain fish species and geographical variability — may also be involved (Lehane and Lewis, 2000). Friedman et al. (2008) reviewed 13 CFP clinical-profile reports from around the world and also found that gastro-intestinal symptoms, paraesthesias and dysaesthesias were commonly encountered. Several workers have noted, however, that, beyond the ‘typical’ presentation of CFP, in which paraesthesias and dysaesthesias are the most important diagnostic indicators (Bagnis et al., 1979; Lewis, 1984; Pearn, 2001), the clinical appearance of ciguatera is complex. Some cases present with only a few symptoms, while others may describe an extensive suite of gastro-intestinal, sensory and non-specific signs and symptoms (Lewis, 2006). The symptom of aberrant temperature perception, sometimes described as ‘paradoxical’ or ‘reversed’ temperature sensation, is not always reported (Friedman et al., 2008). Cold allodynia may be a more accurate descriptor for the often-reported dysaesthesia in which contact with cold objects, floors or fluids elicits unpleasant burning sensations (Cameron and Capra, 1993; Lehane and Lewis, 2000; Palafox and Buenconsejo-Lum, 2001; Isbister and Kiernan, 2005). An important constraint, raised by

several workers discussing the epidemiology of this disease, is that, in the absence of a confirmatory diagnostic test, CFP is a clinical diagnosis, so diagnostic biases towards ciguatera-specific symptoms may come into play. Dissimilar epidemiological and case definitions across different regions and centres may also impact on the global understanding of CFP epidemiology (Bagnis et al., 1979; Morris et al., 1982a; Neville and Warren, 2003).

A remarkable feature of ciguatera poisoning is the occasionally prolonged course of the disease. The initial gastro-intestinal illness, while sometimes severe, is usually self-limiting and resolves after a few days. Cardiac signs and orthostatic hypotension, when present, can last for longer periods but in some cases an extended course of the illness is seen, with one or more of various symptoms — intense pruritus, lassitude and weakness, limb paraesthesias and/or dysaesthesias, arthralgia and/or cold allodynia — lasting for weeks, months or sometimes years (Frenette et al., 1988; Lehane and Lewis, 2000; Palafox and Buenconsejo-Lum, 2001; Pearn, 2001; Friedman et al., 2008). The reasons why such a prolonged course of illness can occur in CFP are incompletely understood. The highly lipophilic nature of the ciguatoxins (the toxins may be slowly released from fat stores into the circulation) and their potency (i.e. their ability to cause illness at extraordinarily low concentrations) may offer some explanation (Lehane and Lewis, 2000; Nicholson and Lewis, 2006). The severity of the initial illness may not be a reliable predictor of the time needed for full recovery; severe acute intoxications, requiring admission to an intensive-care unit, may progress to complete recovery from all symptoms within a few weeks, whereas some less acutely severe CFP cases may take much longer to become asymptomatic. While dose-related matters (the weight of fish consumed, the subject's bodyweight, and the proportion of the ingested dose lost via vomiting) must be considered, and contrasting responses to different ciguatoxin congener profiles in contaminated fish may be seen, the reports of unusually variable clinical presentation in CFP highlight the complex and somewhat unpredictable nature of the disease.

Individuals who are unaffected or suffer only gastro-intestinal illness, in outbreaks that are otherwise typical of CFP, are mentioned in several reports (Cooper, 1964; Morris et al., 1982a; Frenette et al., 1988). In some cases, the severity and/or duration of CFP symptoms appear unrelated to the amount of suspect fish consumed (Mitchell, 1981; Katz et al., 1993; Swift and Swift, 1993; Glaziou and Legrand, 1994; Palafox and Buenconsejo-Lum, 2001; Langley et al., 2009). These observations indicate that typical dose–response relationships may not always apply; in some cases, complex gene–environment interactions may influence the disease process. Tolerance to ciguatera in some individuals has been claimed, although such reports are incomplete and anecdotal (Cooper, 1964). A greater spread of empirical evidence indicates that immunological tolerance to ciguatoxins does not develop; indeed, a hypersensitivity-like phenomenon is more often described, where exacerbation or recurrence of sensory neurological symptoms that had otherwise resolved is triggered by consumption of alcohol, coffee, tea or foods such as fish, poultry, pork, chocolate or nuts (Cooper, 1964; Morris et al., 1982a; Lewis, 1984; Russell and Egen, 1991; DiNubile and Hokama, 1995; Lehane and Lewis, 2000; Palafox and Buenconsejo-Lum, 2001; Lewis, 2006; Achaibar et al., 2007). The exacerbation of symptoms by alcohol or coffee drunk during the acute phase of the illness has also been reported (Swift and Swift, 1993; Asaeda, 2001; Achaibar et al., 2007). Compared with first-time poisonings, repeat ciguatera intoxications (which are encountered particularly across South Pacific island nations that are substantially reliant on seafood as a major dietary component) appear to be associated with more symptoms and with more severe symptoms (Tonge et al., 1967; Bagnis et al., 1979; Morris et al., 1982b; Lewis, 1984; Glaziou and Martin, 1993; Glaziou and Legrand, 1994).

The distressing and disabling nature of the symptoms of acute and sub-acute ciguatera poisoning should not be underestimated or trivialized. John Pearn, a distinguished Queensland clinician, medical researcher and polymath, took an early and abiding interest in ciguatera poisoning. He observed (Pearn, 2001) that, in the disease, fluids, either applied to the skin or eliminated from the body, can initiate excruciating discomfort:

> "Warm fluids are particularly distressing and showering or bathing may be too painful to endure by some severely poisoned victims. I have seen adult cases with such heightened nociperception … that victims are reduced to shocked weeping in the context of unbearable distress during micturition or breast feeding."

Fluid ingestion can also provoke distressing sensory responses, in and around the oral cavity: many case reports and reviews describe unusual burning or electric-shock-like dysaesthesias, particularly when cold drinks are taken (Lee and Pang, 1945; Swift and Swift, 1993; Fenner et al., 1997; Lucas et al., 1997; Arnett and Lim, 2007). CFP-related pruritus, whether generalised or localised, can be intense and unremitting and, like other neurogenic and neuropathic itches (Yosipovitch et al., 2003), can have a significant adverse impact on quality of life.

## CIGUATERA-RELATED SEXUAL DYSFUNCTION

In the true sense of what some authorities (Lewis and Ruff, 1993; Ting et al., 1998) describe as the protean nature of ciguatera poisoning, a number of reports of ano–genital pain, discomfort and dysfunction can be found in the literature. Proctalgia was reported by at least one of the sailors who were probably afflicted by ciguatera poisoning on Captain Cook's voyages in the South Pacific (Doherty, 2005). "Intense" penile pain after defecation (Ting et al., 1998), three cases of testicular pain (Tonge et al., 1967; Ting et al., 1998) and a 5-year-old boy who suffered "severe agony and disturbed sleep … due to pain in the tip of his penis" (Mitchell, 1981) have been described. One adult male reported that his testicles "felt big and heavy" even though there were no clinical signs of testicular enlargement or oedema (Lee and Pang, 1945). Eight of 19 sexually active individuals, when questioned, reported that their CFP symptoms were exacerbated during sexual activity (Lange et al., 1992). Two of these cases were men who experienced painful ejaculation, one of whom apparently found the experience so unpleasant that he abstained from further sexual activity for "several" months (Lange et al., 1989). More recently, six of seven sexually active CFP cases reported painful intercourse: two males with painful ejaculation and four females with dyspareunia — specifically, burning sensations during and up to 3 h after coitus (Langley et al., 2009). Severe penile or pubic pain during erection and ejaculation are noted in other reports on male cases (Pearn et al., 1989; Swift and Swift, 1993; Ting et al., 1998; Farstad and Chow, 2001). Yet another case report describes a man whose "penis was extremely sensitive, which caused occasional ejaculations" (Villareal et al., 2006). Intense and distressing vulval pruritus was reported by a 14-year-old female with CFP (Delord et al., 1984). Painful dysuria is another, albeit infrequently reported, symptom of ciguatera intoxication (Tonge et al., 1967; Ng and Gregory, 2000; Neville and Warren, 2003; Kipping et al., 2006; Friedman et al., 2008), although this condition is not necessarily associated with symptoms affecting sexual function; one of the men discussed above experienced painful ejaculation, whereas he found both bowel and bladder evacuation to be painless (Swift and Swift, 1993).

Signs of ciguatoxin-related genito–urinary dysfunction in mammals other than humans are not commonly reported in the literature, presumably because it is difficult to assess such specific sensory faculties in such animals. Priapism was observed in the otherwise very ill dogs that had been fed the viscera of (presumably) ciguatoxic fish on Cook's Pacific voyage of 1774 (Doherty, 2005). Priapism and penile thrombus formation were observed in mice experimentally dosed with ciguatoxins for subsequent histopathological investigations; terminal erections that were maintained post-mortem were seen (Terao et al., 1991). Again in mice, penile cyanosis, paroxysmal erection, incomplete erection and priapism were noted by workers who were developing a mouse bioassay for ciguatoxins (Vernoux, 1994). Some of the male mice used by a team in Mexico for a ciguatera bioassay had 'intense inflammation of the scrotum that lasted even after death' (Lechuga-Devéze and Sierra-Beltrán, 1995).

An interesting supplement to the discussion of acute sexual dysfunction are the observations, from three separate reports, of the apparent transmission of ciguatera-related

symptoms — both localised and systemic — to the sexual partners of CFP cases (the sexual partners not having eaten any ciguatoxic fish). Lange et al. (1989), for example, noted that, after coitus, the wives of two men with acute ciguatera poisoning experienced "deep pelvic and vaginal burning and stinging" that persisted for up to 3 weeks. As one of these men was the aforementioned individual who subsequently avoided further sexual activity because of painful ejaculation, the weeks-long dyspareunia experienced by these women may — in one case at least — have resulted from a single sexual encounter (Lange et al., 1989). Ting et al. (1998) subsequently described the nausea, circum-oral dysaesthesia, pruritus, arthralgia and lassitude that occurred, following vaginal intercourse, in the female sexual partner of another man with CFP. The posited exposure route here, as also suggested by Lange et al. (1989), is that of ciguatera toxins transferred via seminal fluid, presumably in the lipid component. Female-to-male transfer of ciguatera symptoms is implied from a report of a man who experienced penile pain — described as "pain … at the tip of his penis" — following sexual intercourse with his wife; the wife had consumed ciguatoxic fish, whereas her husband had not (Geller et al., 1991). These reports indicate that ciguatera toxins can be transferred, via physiological fluids, across the skin and mucous membranes. This is consistent with other reports in the literature that describe paraesthesias on the hands and fingers of individuals who have been preparing, for consumption, fish that was subsequently found to be ciguatoxic (Mitchell, 1981; Lehane and Lewis, 2000).

Although sexual dysfunction is infrequently described in the context of CFP (Anon., 2009), the topic has not been investigated systematically; it may be the case that under-reporting and/or under-elucidation of such symptoms may be occurring because of the highly personal and sensitive nature of the condition. It may be helpful to characterise the frequency and extent of acute sexual dysfunction and its quality-of-life impacts through descriptive epidemiological investigation of CFP cases, using questionnaire and interview techniques refined by sexual-health experts, with appropriate ethical oversight.

## CLINICAL MANAGEMENT AND TREATMENT

Although a definitive antidote for CFP is not yet available clinically, an international research programme is investigating the properties of brevenal, a cyclic polyether produced by the dinoflagellate Karenia brevis. Brevenal appears to act as a nontoxic antagonist of brevetoxins — harmful algal-bloom toxins responsible for the food-borne neuro-intoxication syndrome known as neurotoxic shellfish poisoning — at their receptor site on voltage-gated sodium channels (VGSC). Because ciguatoxins occupy the same VGSC binding site as brevetoxins, there may be significant potential for brevenal to function as a pharmacotherapy for CFP (Mattei et al., 2008; Nguyen-Huu et al., 2010). Brevenal has recently been synthesised (Takamura et al., 2009) but it remains to be seen whether or when the molecule can be produced efficiently on a commercial basis, to facilitate drug development. A general problem with many biologically-active marine algal and cyanobacterial natural products is that they possess multiple ring structures and chiral centres and so require complex, multi-step synthesis.

In the absence of a specific pharmaceutical intervention for CFP, treatment has been supportive and directed towards the relief of symptoms. Severe intoxications may require ventilatory and haemodynamic support in the acute stage (Crump et al., 1999; de Haro et al., 2003; Friedman et al., 2008). Intravenous atropine can be used to treat any bradycardia (Geller et al., 1991; Hung et al., 2005). Tricyclic antidepressants, selective serotonin re-uptake inhibitors (SSRI), benzodiazepines, anticonvulsants, antihistamines, analgesics, oral and topical steroids and topical antipruritics have all been used to treat various CFP-related symptoms, such as fatigue, arthralgia, pruritus, paraesthesias and dysaesthesias, with variable responses (Lee and Pang, 1945; Delord et al., 1984; Geller et al., 1991; Lange et al., 1992; Eastaugh, 1996; Crump et al., 1999; Friedman et al., 2008; Schwarz et al., 2008). Gabapentin, developed as an anticonvulsant for the management of focal epilepsy, has also been used to treat neuropathic pain and may also help to relieve neuropathic pruritus (Yosipovitch et al.,

2003; Finnerup et al., 2010). In their report, Perez et al. (2001) describe the rapid relief of symptoms in two CFP cases given gabapentin, the trial cessation of the gabapentin therapy being followed, within hours, by the return of symptoms.

The indigenous pharmacopeia of the South Pacific has received occasional research attention. Over 90 plants are reported to have beneficial effects in the treatment of ciguatera, although, as with the western pharmacotherapies, traditional remedies have largely been directed at relieving particular symptoms (Bourdy et al., 1992; Boydron-Le Garrec et al., 2005; Nicholson and Lewis, 2006). There does not appear to be an ethnobotanical "cure-all" for ciguatera poisoning. Neither traditional nor modern drug treatments for the relief of ciguatera symptoms have been subjected to clinical trials.

The one pharmacological intervention for CFP that has received a good deal of clinical and research attention is that of mannitol, an osmotic diuretic agent. Mannitol was first used in the Marshall Islands to treat two neurologically obtunded CFP patients in whom cerebral oedema (the routine management of which would include a mannitol infusion) was suspected. These patients made a rapid and remarkable return to consciousness and recovery. The clinicians involved then proceeded to treat a further 22 CFP cases with intravenous mannitol, again reporting an impressive resolution of symptoms (Palafox and Buenconsejo-Lum, 2001). Centres in other ciguatera-prone regions across the world subsequently used mannitol therapy, publishing similar findings in case reports, case series and the results of non-randomized trials (Pearn et al., 1989; Williamson, 1990; Stewart, 1991; Blythe et al., 1994; Eastaugh, 1996; Mitchell, 2005; Schwarz et al., 2008). In a randomized, non-blinded study conducted in New Caledonia and Tahiti, CFP cases were allocated to either mannitol infusion ($n$=34) or intravenous glucose with added vitamins ($n$=29). The mannitol-treated group experienced a significant improvement in symptom scores compared with the other group (Bagnis et al., 1992). Conversely, in their randomized controlled trial covering 50 CFP patients, Schnorf et al. (2002) found that an infusion of physiological saline was as good as one of mannitol in terms of the resolution of symptoms. The authors of that study and others (Schnorf et al., 2002; Isbister and Kiernan, 2005) concluded that the recoveries observed in both the mannitol- and saline-treated groups implied that most people with acute CFP will recover without treatment. Some aspects of the trial by Schnorf et al. (2002) were subsequently reviewed by Friedman et al. (2008). For example, one in every four of the patients treated with mannitol was infused a long time (69 h–28 days) after the onset of CFP symptoms, and exposure misclassification was possible because CFP diagnosis was based only on clinical presentation, without the confirmatory detection of ciguatera toxin in the fish consumed by the study subjects (reliance on the clinical diagnosis of CFP may potentially have influenced other epidemiological investigations).

A further observation made in the study by Schnorf et al. (2002), that any future clinico–epidemiological assessment of mannitol in CFP should address, is that of the high incidence of pain or discomfort at the injection site among the subjects given mannitol (84%, compared with 36% of the patients infused with saline). Such adverse effects have the potential to undermine the investigator-blinded status of a trial, if not the subject-blinded aspects. This problem could probably be overcome by the use of large-bore intravenous cannulae sited more proximally (e.g. in the antecubital fossa). Pre-injection with lignocaine and/or metoclopramide may also be worth investigating in this context, possibly in a pilot evaluation; these agents appear to be valuable in preventing or reducing the injection-site pain caused by propofol, an intravenous anaesthetic (Fujii and Nakayama, 2007; Fujii and Itakura, 2008). A future reassessment of the efficacy of mannitol in CFP might also consider alternate approaches to randomized trials, specifically the use of 'n-of-1' trials. Such trials make use of a multiple crossover design in a single patient, to compare treatment effects of active therapy against placebo; treatments are delivered in random and blinded sequence, with each patient serving as their own control (Mahon et al., 1996; Anon, 1998; Wegman et al., 2006). Although a group-randomized trial can determine average treatment effects, a series n-of-1 studies might be an alternative option for a research programme to reassess the efficacy of mannitol therapy for ciguatera poisoning, given the variable responses to mannitol seen

within and across some CFP case series and case reports (Pearn et al., 1989; Lange et al., 1992; de Haro et al., 2003; Slobbe et al., 2008).

## MANAGEMENT OF CIGUATERA IN QUEENSLAND

The state of Queensland, in north–eastern Australia, hosts the world's largest coral reef system (the Great Barrier Reef) and is, in consequence, a global 'hot-spot' for ciguatoxic fish. Although Australian cases of CFP occasionally occur south of Queensland, in northern New South Wales (where they are caused by locally-captured pelagic fish such as *Sc. commerson*), most outbreaks caused by fish from Australian waters are attributable to fish caught in the seas off Queensland and the Northern Territory. Fish sourced from Queensland have been responsible for ciguatera outbreaks in southern Australian states and internationally (Karalis et al., 2000; Ng and Gregory, 2000; Wong et al., 2005), and overseas visitors to Queensland have contracted the illness (Slobbe et al., 2008). Ciguatera clearly has the potential to tarnish the reputation of Queensland's tourism and fish-export industries.

Queensland's management of CFP encompasses strategies by the fisheries industry, Queensland Primary Industries and Fisheries (part of the Department of Employment, Economic Development and Innovation), and Queensland Health. The Sydney Fish Market, which is the largest centre of fish distribution in Australia, incorporates into its duty-of-care provisions guidelines to prevent high-risk fish from entering the wholesale market. This approach rejects for sale fish from restricted-supply regions in Queensland and sets maximum size limits for certain high-risk ciguatera vectors. The Sydney Fish Market guidelines (Anon., 2005) are the *de facto* Australian industry standard, on which the seafood-industry organizations of other Australian states base their approaches to ciguatera risk management.

Queensland Primary Industries and Fisheries has a list of protected and no-take fish species. This list (www.dpi.qld.gov.au/28_14857.htm) embraces species that are vulnerable to over-exploitation as well as species that are potentially harmful when eaten. The ciguatera vectors *Lutjanus bohar*, *L. gibbus* and *Symphorus nematophorus* are included in the no-take list of fish that should not be caught or possessed. The Queensland Government, under the 2008 Fisheries Regulation of the Fisheries Act 1994, also prohibits the capture and possession of barracudas (*Sphyraena barracuda* and *Sp. jello*) and Spanish mackerel (*Sc. commerson*) from Platypus Bay. Platypus Bay, on the north–western (landward) side of Fraser Island, located some 300 km north of Brisbane, has long been known as a particularly localized and concentrated source area for ciguatoxic fish in Queensland waters. The bay is somewhat atypical as a ciguatera source in that it has a sand — not coral — base but investigations two decades ago found high concentrations of resident *Gambierdiscus toxicus* that produce gambiertoxins, which are ciguatoxin precursors (Holmes et al., 1994). The presence of large congregations of toxic *G. toxicus* in Platypus Bay probably explains the unusual contribution of this location to Queensland's ciguatera problem.

Queensland Health's approach to ciguatera poisoning in individuals and common-source outbreaks is centred on ciguatera intoxication being a notifiable condition under the requirements of the 2005 Public Health Regulation of the Public Health Act 2005. Ciguatera cases and outbreaks identified by clinical diagnosis and reported to Queensland Health are investigated by public-health officers, who interview individuals with the illness to elicit information on symptoms and the likely source of the illness, and retrieve any remaining tissues from the fish that was the suspected source of the complaint. Fish samples can be recovered from the individual or family with suspected ciguatera poisoning and/or seized from the retail outlet that supplied the fish. They are sent to the Queensland Health Forensic and Scientific Services (QHFSS) laboratories for the identification and quantification of Pacific ciguatera toxins. In the routine analysis of ciguatoxins, the rapid extraction method recently introduced into these laboratories — that described by Lewis et al. (2009) — has been found to be markedly better than the time-consuming extraction techniques previously used, which involved multiple solvent exchanges and drying steps (Stewart et al., 2010). The analysis of three Pacific ciguatoxin congeners (P-CTX-1, -2 and -3) in these laboratories is

complemented by a DNA barcoding technique that allows the species of fish presented for ciguatoxin analysis to be identified. This allows the problem of fish substitution and misidentification to be assessed, from a public-health perspective. While there appears to be no evidence, from the ciguatoxin-analysis programme or elsewhere, of the systematic mislabelling of fish in Queensland, fish substitution has reportedly been linked to ciguatera intoxication in the U.S.A., through the sale and consumption of mislabelled barracuda (Lange et al., 1992).

Preliminary results from the combined ciguatoxin analyses and fish identifications undertaken at the QHFSS indicate considerable inter-specific variability (or, more accurately, inter-familial variability) in the ciguatoxin congener profiles of fish. Most of the fish samples sent for ciguatoxin analysis, following public-health notifications, have come from Spanish mackerel (*Sc. commerson*). In the Spanish mackerel that have been analysed, P-CTX-1 has been found to be the principal congener in terms of proportional concentration, with P-CTX-2 at either equivalent or lower concentrations to that of P-CTX-1 and P-CTX-3 at very low or undetectable levels. In samples from five serranids (two *Plectropomus laevis*, one *P. areolatus*, one *Variola louti* and one *Epinephelus fuscoguttatus*), however, P-CTX-2 and P-CTX-3 were the main congeners, with P-CTX-1 detected between equivalent and (10-fold lower concentrations.

Because the state of Queensland includes ciguatera intoxication in its register of notifiable diseases, well-established protocols and procedures are in place to retrieve and transport suspect fish to the laboratories of QHFSS for routine analysis of ciguatoxins and species identification. These combined capabilities open up the potential to refine future epidemiological study designs, in particular the ability to tighten the entry criteria for epidemiological investigations. Reliance on the clinical diagnoses of CFP has the potential to introduce exposure misclassification into epidemiological investigations, depending on how case definitions are applied. An ability to recruit subjects whose diagnosis of CFP is always complemented by a submitted fish specimen, with the confirmed detection and quantification of ciguatoxins in that specimen, should advance the understanding of this still under-researched condition. Ciguatera will remain a clinical diagnosis until such time that a confirmatory test, say for blood, is routinely available. The ability to identify ciguatoxins in accompanying fish specimens routinely will, however, allow clinicians and epidemiologists to increase their diagnostic confidence. In the future, investigators working on CFP at QHFSS will explore new ways to utilise the current analytical capability and epidemiological surveillance of ciguatera poisoning. They may be able to contribute to the knowledge base by designing studies to investigate some of the topics discussed in this review, such as the impact of the symptoms of CFP on quality of life and sexual function, and facilitate more valid clinical trials on the efficacy of mannitol and other pharmacotherapies.

Among the fish species known to pose a risk of causing ciguatera poisoning, the larger specimens are reported to be more likely to attain hazardous concentrations of ciguatoxins because they are older and have had more time to accumulate the toxins through their diet (Russell and Egen, 1991; Lehane and Lewis, 2000; Dickey, 2008). In the absence of a reliable, rapid and cost-effective screening test for ciguatoxins, the seafood industry takes a precautionary risk-management approach by — among other strategies — setting upper size limits for the marketing of Spanish mackerel and other known ciguatera vectors, as discussed above. Size-limit restriction is not, however, failsafe, as smaller specimens may be ciguatoxic. The larger but non-toxic fish also represent unrealised economic opportunities. Two large specimens of known ciguatera vectors (both caught by recreational anglers) were recently examined at QHFSS, with the aim of procuring ciguatoxic fish for an ongoing research programme. One of these fish was a bluespotted coral trout (*P. laevis*) while the other was a Spanish mackerel (*Sc. commerson*) of about 30 kg. The mackerel (Fig. 2) was caught by a Queensland Health colleague who is aware of the problem of CFP.

**FIGURE 2.** A recreational angler holding a Spanish mackerel (*Scomberomorus commerson*). The fish, with an intact weight of approximately 30 kg, was caught off Cairns, North Queensland, in August 2010. Image courtesy of B. Milligan.

These fish were tested by routine chemical analysis (Stewart et al., 2010) — a method that is neither cost-effective nor sufficiently rapid to be considered as a screening tool. Although both fish were found to be negative for Pacific ciguatoxins and both turned out to be fine table fish, these specimens would have been rejected for sale by the Sydney Fish Market and other Australian seafood distributors. This demonstrates the as-yet unrealised global potential for a suitable screening test or assay. The ability to screen fish reliably, before sale or consumption, for the presence of clinically-relevant concentrations of ciguatoxins would confer benefits for the protection of public health and open up the economic potential of fisheries that are currently subject to ciguatera-risk constraints based on the somewhat blunt instruments of fish size, species and geographical location.

## CONCLUSIONS

Ciguatera poisoning remains a complex public-health dilemma at the start of the 21st Century. Under-reporting and misdiagnosis are likely to be widespread but difficult to quantify (Lehane and Lewis, 2000; Dickey, 2008; Friedman et al., 2008). There is an unmet global demand for both a confirmatory diagnostic test in humans and a fast, low-cost and reliable screen that can be used to test the safety of fish for consumption. The symptoms of ciguatera poisoning are, in many cases, distressing and disabling, resulting in considerable social and economic costs in terms of lost productivity and quality-of-life impacts (Lehane and Lewis, 2000). Chronic neurological sequelae are reported in a small proportion of CFP cases; the molecular and pathological substrates for chronic neurological disability in CFP are

poorly understood and arguably deserve more research attention. The epidemiological surveillance and clinical management of ciguatera poisoning may well benefit from recent and anticipated advances in analytical capability for the detection and quantification of ciguatera toxins.

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