Ichthyosarcotoxism: poisoning by edible fish

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The term *ichthyosarcotoxism* describes a variety of conditions arising as the result of poisoning by fish flesh. Poisoning by shellfish and other invertebrates is excluded, as is bacterial food poisoning from contaminated fish. Although most of the conditions are experienced mainly in warmer climates than Britain’s, one form of fish poisoning is relatively common here, and others may be imported, either through imported fish or by travellers. The conditions could present to any accident and emergency (A&E) department, and increased awareness of these disease entities may improve diagnosis and management.

It has long been known that some normally edible fish species may from time to time cause poisoning. Many of the early records of these conditions come from the Royal Navy. Both Captain Bligh and Captain Cook described illness among their crews after eating fish which were known usually to be safe. The first detailed medical treatise on fish poisoning in the West Indies was written by the Surgeon on a frigate. Since the beginning of this century, interest in the conditions and awareness of the considerable morbidity they produce has increased. Several different clinical syndromes have been described with a variety of gastrointestinal, neurotoxic, and cardiotoxic features.

The syndromes are not specific to any one species of fish—some species may at times cause different syndromes, and even within a recognised single disease entity there may be wide variation in symptoms depending on the fish eaten or the geographical area. All of this makes classification very difficult and consequently no recognised classification exists. Table 1 shows an attempt to classify the conditions by the type of clinical features and symptoms usually seen. This arrangement is simplified and there is some overlap between conditions, but for the physician faced with a patient with likely fish poisoning it gives some guidance towards a specific diagnosis.

It has been suggested that the features of ciguatera, tetraodon, and paralytic shellfish poisoning are similar and that these should be considered as a single disease, pelagic paralysis. However, each of these syndromes produces a recognisable clinical picture, the toxins causing the conditions have been shown to be different, the fish species implicated vary, the morbidity and mortality are differ greatly, and there are differences in recommended management. For these reasons most authorities agree that the conditions should be considered as distinct entities.

Most of these conditions are found mainly in tropical and subtropical regions, but scombroid is well known and endemic in the United Kingdom. Ciguatera has been described in West Indians returning to Britain and in British servicemen. “Exotic” fish are increasingly

<table>
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<tr>
<th>Table 1</th>
<th>Classification of ichthyosarcotoxins</th>
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<tr>
<td><strong>Group 1</strong></td>
<td>Mild gastrointestinal symptoms only</td>
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<tr>
<td>Cyclotomus (lampreys and hagfish). Probably from slime. Severe but self-limiting symptoms.</td>
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<tr>
<td>Elasmobranch (shark flesh usually from Greenland sleeper shark). Relatively mild.</td>
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<tr>
<td>Gemephyrid (snake mackerel, castor oil fish, skilfish). Strongly purgative.</td>
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<td><strong>Group 2</strong></td>
<td>Gastrointestinal and neurological symptoms</td>
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<tr>
<td>Tetraodon (puffer and porcupine fish). See text.</td>
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<tr>
<td>Elasmobranch (shark, liver) (shark liver from most sharks). Possibly related to hypervitaminosis A but probably also some toxin involved.</td>
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<tr>
<td>Ichthyotoxinosis (roe or caviar poisoning). Often freshwater fish including sturgeon and salmon. Related to saxitoxin, the cause of paralytic shellfish poisoning.</td>
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<td><strong>Group 3</strong></td>
<td>Gastrointestinal and cardiac symptoms</td>
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<tr>
<td>Clupeototoxin (sardines, anchovies, herring). Episodic outbreaks.</td>
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<tr>
<td><strong>Group 4</strong></td>
<td>Gastrointestinal, neurological, cardiac, joints, etc</td>
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<tr>
<td>Ciguatera (many fish and symptoms). See text.</td>
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<tr>
<td>Gymnothorax (Moray eel). Probably severe ciguatera.</td>
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<td><strong>Group 5</strong></td>
<td>Anaphylactoid</td>
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<tr>
<td>Scombroid (See text)</td>
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<tr>
<td><strong>Group 6</strong></td>
<td>Hallucinogenic</td>
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<tr>
<td>Chimera (rattfish and elephant fish). Very poorly understood. Avoid these fish!</td>
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<tr>
<td>Hallucinogenic fish poisoning (HFP) (mainly mullet). See text.</td>
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</tr>
<tr>
<td>Surgeon fish. Possibly related to one of ciguateric toxins (maitotoxin) but more likely to be indole induced.</td>
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available in British supermarkets, and international cuisine gains popularity making it possible that tetrodotoxication will soon be seen in Europe. These three conditions are certainly the most important ichthyosarcotoxins worldwide, but before discussing these in more detail, two of the less common are worthy of particular mention.

**Sardine poisoning**
Sardine poisoning occurs infrequently and episodically in the tropics and as far north as the Mediterranean. For some uncertain reason, suddenly many of the sardines in a local area, usually those caught close to shore, appear to be toxic at the same time. Sometimes anchovies and sprats many also be affected.

**CLINICAL FEATURES**
A violent gastrointestinal illness precedes paraesthesiae, progressive paresis, fits, and tetanic spasms. Cardiovascular effects are often marked, with arrhythmias and even cardiac arrest. Behavioural changes with anxiety and bizarre behaviour are also frequent. Desquamation and other skin problems are reported in those who survive the acute episode. Mortality is about 40%.

**PATHOGENESIS**
It has been suggested that the occurrence of sardine poisoning may be associated with algal blooms such as the red tides which cause saxitoxin problems in shellfish, but this has not been established. A hypothetical toxin involving the conversion of eicosapentaenoic acids to a toxin akin to thromboxane A2 has been postulated.

Given that all the fish involved feed on plankton, it seems likely that a protozoan is the origin of the toxin (as in ciguatera and paralytic shellfish poisoning), but the exact organism has yet to be identified.

**TREATMENT**
No effective treatment has been described, and given the high mortality, work is required to try to produce an effective prevention strategy or treatment.

**Hallucinogenic fish poisoning**
While sardine poisoning causes bizarre behavioural changes, another interesting group of ichthyotoxins is known to produce hallucinations without gastrointestinal or other toxicity. Various toxins including indoles akin to LSD have been implicated, with sources in algae and plankton eaten by the fish. There is some evidence that a combination of these toxins with plant and perhaps fungal toxins is the basis for the “zombies” of Haiti.

**Scombroid**
The only indigenous British ichthyosarcotoxism derives its name from the type of fish in which it was originally described. The scombroid fish are the dark fleshed migratory species such as mackerel, tuna, and bonito. Cases of this poisoning have been described after the ingestion of non-scombroid fish such as herring, sardines, anchovies, and salmon. Perhaps therefore the alternative name of “anaphylactoid fish poisoning” should be used.

**CLINICAL FEATURES**
The clinical picture starts with rapid onset of symptoms, sometimes within 10 minutes of beginning to eat the fish. Symptoms are usually maximal at about two hours after ingestion. An acute gastrointestinal upset with vomiting, abdominal cramps, and sometimes diarrhea is associated with erythema, urticarial patches, and oedema. Although much of the swelling is often facial, airway compromise is rare. There can be tachycardia and palpitations, although these are uncommon. The disease is frightening and distressing but is very seldom if ever fatal. Spontaneous recovery within 24 hours is usual without treatment, but appropriate management can dramatically curtail the attacks.

**AETIOLOGY**
Smoked Mackerel used to account for most of the outbreaks of this condition in the United Kingdom, but tinned products, mainly tuna and sardines, now appear to cause more problems.

In 1993 thirty two incidents were reported in the first eight months of the year. Seven of these were traced to two batches of imported fresh tuna from Indonesia and Sri Lanka, and 10 were from canned products.

There is probably considerable under-reporting of scombroid for several reasons. The disease is self limiting and may not come to medical attention. Even if it does it may not be recognised, the symptoms being easily confused with allergy. There is no legal requirement to report the condition, although the Food Hygiene Laboratory at PHLS (Public Health Hygiene Laboratory) would welcome reports.

**PATHOGENESIS**
The pathogenesis of scombroid remains a matter of some dispute. The flesh of the implicated fish is rich in histidine, and organisms such as klebsiella and morganella in gut and bile produce a decarboxylase which converts this to histamine, and possibly other amines such as saurine. Since the symptoms produced are those usually associated with histamine release, it is considered by many that histamine is the principal toxin. Some investigators, however, have suggested that since histamine can be taken by mouth without ill effect, and since the symptoms are not necessarily related to the amount of histamine in the fish, a more complex mechanism involving the activation of mast cells by the toxin may be involved.

**TREATMENT**
In the past treatment relied on adrenaline and histamine (H1) antagonists on the assumption that the condition was histamine induced. Recent experience has suggested that H2 receptors may play some part in the aetiology and the use of intravenous cimetidine has been recommended, producing very rapid resolution of all symptoms.
PREVENTION
This condition should be completely preventable. It is poor handling and storage of fish at too high a temperature which allows the enzymatic activity to progress. The reduction in the cases attributed to smoked mackerel is testimony to the results possible with improvement in food hygiene. A case can be made for compulsory measurement of histamine levels in imported canned products, as is already done in Sweden, but in view of the debate about pathogenesis and the difficulty in agreeing what a permitted level should be there are currently no plans to introduce this in the United Kingdom. Histamine concentrations can, however, be measured in suspect fish. Fresh fish should be frozen, and all samples (10 g) should be sent, together with details of the product and the incident, to Anne Scoging at the Food Hygiene Laboratory (telephone 0181 200 4400).6

Tetrodion
The ingestion of toxic pufferfish (and a few other related species) is most common in Japan, where fugu (raw pufferfish) is considered a great delicacy. Cases from deliberate ingestion (usually of ovary) and accidental consumption have also been reported. In Japan only specially licensed chefs are allowed to prepare fugu. Nevertheless there are still several tens of cases every year, and despite much experience in managing these cases the overall mortality is still in excess of 50%.23 24

CLINICAL FEATURES
Shortly after the ingestion of toxic fish, the patient develops a severe gastrointestinal upset with profound vomiting. This is associated with paraesthesiae, ataxia, and paresis which is often rapidly progressive and may lead to respiratory insufficiency. Petechial haemorrhages and extensive haemorrhagic blistering of the skin may progress to severe desquamation. Patients usually lose consciousness rapidly and prolonged convulsions may occur. The severity of attacks has been classified into four grades.25 Death has been reported in as little as 17 minutes from the onset of symptoms, but is usually within hours.25 26

TREATMENT
In severe cases early intensive care is required if there is to be any hope of survival. Even in mild cases hospital admission is essential. Supplementary oxygen should be given, and ventilatory support considered if monitoring suggests respiratory insufficiency. Profound bradycardia, heart block, and circulatory failure can occur, necessitating the use of atropine and inotropes. Emesis can be controlled by continuous low pressure gastric suction rather than by drugs. In early cases gastric lavage using a 2% bicarbonate solution has been suggested and charcoal has been used, on the theoretical basis that it should bind the toxin, but there is no firm evidence for its efficacy. Crystalloid infusion is recommended.24 25 27

PATHOGENESIS
The principal toxin, tetrodotoxin (or TTX), is probably the best understood ichthyotoxin, having been first identified in 1948.28 Other substances such as saxitoxin have been found in the flesh of implicated fish, suggesting that several substances may be involved.29 Tetrodotoxin is a powerful axonal blocking agent which may react with cytochrome systems. It is the most powerful emetic known, and a powerful respiratory depressant, hypotensive agent, and sedative. It causes hypothermia and alters coagulation, and at high doses is a convulsant.21 24 27

Tetrodotoxin is an extremely potent agent and has excited interest as a potential therapeutic tool. There is considerable work on its usefulness in anaesthesia and intensive care, but no standardised preparation or indication yet exists.

PREVENTION
Theoretically tetrodion poisoning should be preventable simply by avoiding the known toxic species. Avoiding the contamination of fish flesh with gut contents, visceral, and ovarian tissue would go a long way to controlling the severity of any case, but, as has been shown in Japan, even careful control of preparation cannot completely prevent the disease. Perhaps cultural differences will prevent the European patient population from risking exposure to such a potent toxin. As yet, there has been no reported case in the United Kingdom, where the sale of fugu is not allowed, but Japanese restaurants and sushi are growing in popularity. There is at least one Japanese licensed chef in this country who has recently been vociferous in the media about his wish to produce this “delicacy” for his London customers. Cases have been seen in California from fish imported from Japan.29 Perhaps fugu in Britain will be next, unless it remains proscribed.

Ciguatera
 Probably the most prevalent ichthyosarcoxicism worldwide, and a well recognised cause of considerable morbidity in the tropics and sub-tropics, ciguatera takes its name from “cigua”, the Cuban name for a form of sea snail (or turban shell) which was initially linked with this condition.26 The true incidence is not known, as many local people do not seek medical attention. The incidence in Hawaii has been estimated at about 3/100 000, while a telephone survey in Queensland in the 1980s suggested an annual incidence of about 1800/100 000.31 The highest risk area appears to be in the eastern Pacific, and particularly in French Polynesia, although the disease is widespread throughout the tropics and adjacent zones, and is frequently reported in Australia, the United States, and the Caribbean.32 33

The disease has been seen in Britain in people who have eaten fish shortly before leaving the Caribbean to return to this country, and in one case where fish was brought back to the United Kingdom.10 The increasing availability
of tropical seafish in supermarkets suggests that the disease could become more common.\textsuperscript{36-38}

Etiology
In each area where ciguatera occurs there is considerable variation in the toxicity of fish from different reefs, with the toxicity of any given reef altering over time.\textsuperscript{35-39} Disturbance, whether by natural events such as earthquakes or by man (beam trawling), appears to allow an increase of toxicity in the disturbed area.\textsuperscript{7} Over 400 fish species have at one time been implicated in the pathogenesis of ciguatera,\textsuperscript{1} but probably only about 50 species, mainly the larger carnivores, cause most of the problems. Grouper, snapper, barracuda, surgeon fish, and Moray eel are probably the most common ciguotoxic fish (figs 1-3).\textsuperscript{33,36} Until fairly recently Moray eel was thought to cause a much more serious disease than ciguatera, which was called gymnothorax poisoning. It is now considered that gymnothorax is simply a more severe form of ciguatera due to much higher concentrations of the toxins in Moray flesh than in any other fish.

It is likely that apparent geographical and ethnic differences in the symptoms of ciguatera reflect, at least to some extent, variations in dietary preferences.\textsuperscript{22}

Clinical Features
The clinical disease usually starts about four to 10 hours after ingestion of toxic fish, with gastrointestinal effects of nausea, vomiting, and diarrhoea. It varies considerably in severity, but is often quite mild. The degree of this upset seems to be correlated with the ingested dose of toxin and may give an early indication of the likely severity of the episode.

Some hours later paraesthesiae, dysaesthesiae, headache, malaise, weakness, pruritus, and a host of other symptoms develop. Some 300 symptoms and signs have been described.\textsuperscript{4} Cardiotoxicity may also occur, with heart block the most common finding.\textsuperscript{7,11,36} The feature which appears to be almost pathognomonic of ciguatera is a strange reversal of temperature discrimination, such that hot objects feel cold and vice versa. This is often most noticeable in the mouth, where hot drinks seem cold and ice “burns”, but the symptom does not usually develop for two to five days and is therefore not much help in making the diagnosis in the A&E department.

The neurotoxic symptoms are long lasting, with many patients reporting persistent problems three months after the incident. A chronic form of the condition may occur (notably in Melanesia) characterised by remission and relapse in which ataxia and muscle weakness are prominent debilitating features.\textsuperscript{35,39} During the acute episode, patients often describe exacerbations of symptoms after drinking alcohol and after eating fish known not to be toxic, including fish from European waters. Nuts and shellfish have also been implicated in increasing symptoms (Sims JK, personal communication). This may suggest that there is a “cotoxin” in these substances.\textsuperscript{11}

The high incidence, long duration, and debilitating nature of this illness makes it an important condition in endemic areas in terms of morbidity and in its socioeconomic consequences. Overall mortality is, however, very low with the reported death rates being well below 1:1000.

Pathogenesis
In 1977 a substance was isolated from toxic fish which caused the symptoms of ciguatera in animals.\textsuperscript{23,40} This substance, ciguatoxin, was...
found to be produced by a dinoflagellate protozoon (*Gambierdiscus toxicus*), and the appearance of this organism correlated well with the onset of toxicity around particular reefs. Subsequent work has identified at least two other toxins, maitotoxin and scaritoxin, which can be associated with the disease. Other dinoflagellate protozoa such as coolia, prorocentrum, and others can also produce these toxins. The toxins have been demonstrated in increasing concentrations through the food web of vegetarian and carnivorous fish. Some fish appear to be unaffected by the toxin, simply concentrating it in their flesh, while others may themselves be poisoned. These are then ultimately eaten by man, producing the clinical picture of ciguatera. Variations in the concentration of each individual toxin, as well as the total dose ingested, probably account for considerable variations in the severity and overall clinical presentation in individuals.

All the toxins share certain common properties. They are extremely stable substances, resistant to all usual forms of food preparation, storage, and cooking, and pass unchanged into man via the gastrointestinal tract. All the toxins seem to alter the membrane properties of excitable cells in a way that activates voltage dependent sodium channels, which are widespread in nerve and muscle.

**TREATMENT**

Some have suggested prevention of toxin absorption by gastrointestinal tract cleansing (Sims JK, personal communication) but recently the use of magnesium containing cathartics has been implicated in the worsening of symptoms. There is theoretical and anecdotal evidence for the efficacy of activated charcoal in limiting absorption, but no controlled trials have been published.

Most treatment is supportive and aimed at relieving the symptoms. Dehydration and hypovolaemia may occur, and intravenous fluid is recommended. There may also be decreased cardiac output, and correction of bradycardia with atropine and inotropic support with dopamine have both been used successfully. Calcium salts have been used to try to counter some of the ion shifts in nerve cells. Calcium has been shown to be effective in vitro but again only anecdotal evidence for its efficacy in vivo exists.

There are few controlled trials of treatment in this condition and results are difficult to interpret. This makes firm recommendations equally difficult. There are uncontrolled trials in which both calcium and mannitol appear to be effective, the latter probably slightly more so, and its use is therefore recommended in severe cases.

The membrane stabilising effect of amitriptyline may relieve the symptoms, especially dysaesthesiae and pruritus, and it may also be beneficial in the chronic form. Non-steroidal anti-inflammatory drugs may also be of benefit in the early stages (Sims JK, personal communication). Many other drugs have been used, with varying effects, but there is a need for controlled trials to find a specific treatment with minimal side effects.

**PREVENTION**

Given the variety of potentially toxic fish and the difficulties in identifying toxic reefs and fish, prevention is very difficult. Several assays have been tried and a rapid "stick" test for ciguatoxin based on enzyme immunoassay is commercially available and has some use in highly endemic areas. There have been difficulties in validating this test, however, and even in fish markets it is only economically possible to batch-test catches from specific areas, rather than detecting the problem in individual fish. In the USA many ciguatoxic fish are caught by sport fishermen and do not pass through commercial premises where such a test might be possible.

Some investigators have suggested that usually large specimens of any given fish are likely to harbour greater concentrations of the toxins and should be avoided. This, however, does not make economic sense to the fisherman or vendor. Much work is in progress in the attempt to find a cheap reliable way of detecting ciguatoxin in fish flesh. Until this becomes available, however, the advice to travellers in endemic areas should be:

1. Be circumspect about eating fish;
2. Never eat Moray eel or scaleless fish, and avoid anything which the locals don't eat;
3. Avoid particularly big specimens;
4. Don't eat the head, liver, gonads, or viscera of any fish;
5. If you become ill after eating fish seek medical attention.
Summary

The ichthyosarcotoxins are a varied and complex group of conditions which cause a wide variety of symptoms after the ingestion of fish. The diagnosis is largely clinical and all are probably underrecognised and underreported. They pose considerable challenges to clinicians, ecologists, biologists, and others. There is a need for further research into methods of prevention as well as treatment. With increasing air travel and holidays further afield, together with changing eating habits at home, these conditions may become more prevalent in the United Kingdom. I would be interested to hear from anyone who has encountered any of these conditions, and ciguatera in particular.
