are lacking. In a recent study,[5] these two methods compared very well, although over a wide range of proteinuria nephelometry measured on average 20% lower than RIA. Our study confirms this impressive correlation, but found a smaller difference (7%) between the measurements in the normo- and micro-albuminuria range.

Since nephelometry is a far simpler, non-isotope method, widely available and hence less expensive, we suggest that it should become the method of choice to measure MA. We could not confirm previous results[6] suggesting that albumin adsorbs to plastic surfaces, thus causing falsely low levels of albumin when urine is stored in such containers. We did confirm, however,[7] that at least in a minority of samples (5%) freezing at –20°C and thawing decreased albumin levels markedly. It has been suggested that this phenomenon is associated with the formation of precipitates consisting mainly of urates[7] and that it can be prevented by adjusting the pH of urine to neutral either before or after deep-freeze storage.[8]

We conclude that nephelometry can be used for the accurate measurement of MA in diabetic subjects. Urine can be safely stored for up to at least 1 week at 4°C in either plastic or glass containers.

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Scombroid poisoning

Case series of 10 incidents involving 22 patients

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Summary

Scombroid poisoning is a form of ichthyosarcotoxism caused by the consumption of 'spoiled' fish of the dark meat varieties. It can be considered a mild-to-moderate form of 'food poisoning' and it occurs world-wide. Ten incidents, involving 22 patients, were reported to Tygerberg Hospital Pharmacology and Toxicology Consultation Centre in the first quarter of 1990. Cape yellowtail (*Seriola lalandii*) was involved in all the cases. The presenting symptoms and signs (in order of frequency) were: skin rash, diarrhoea, palpitations, headache, nausea and abdominal cramps, paraesthesia, an unusual taste sensation and breathing difficulties. The patients responded well to antihistamines and, in most, the condition resolved within 12 - 24 hours.

Although histamine plays an important role in the pathogenesis of scombroid poisoning, the exact mechanism is still unresolved. The condition should be recognised and not confused with a true seafood allergy. Health workers are urged to alert the authorities when outbreaks of suspected cases of scombroid poisoning are encountered in order to establish the possible cause and to prevent further cases.

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Scombroid poisoning (also referred to as histamine food poisoning) is a form of ichthyosarcotoxism caused by the consumption of 'spoiled' fish, which has undergone autolytic changes as a result of improper storage conditions.[1-4] The term 'scombroid poisoning' originates from the fact that spoiled fish from the family Scombridae (e.g. tuna, mackerel and bonito) were originally implicated in incidents of this type of poisoning.[1] However, it seems that non-scombroid fish are also involved, and on rare occasions even certain cheeses.[1] (Table I summarises fish species which may be implicated in scombroid poisoning.)

Clinically, scombroid poisoning resembles a histamine-like or acute allergic reaction.[1] Most cases are mild and self-limiting, even without treatment. Serious complications are rarely encountered and no deaths have been reported in recent times.[1,5]

Scombroid poisoning occurs world-wide.[2] Between 1968 and 1986 a total of 188 outbreaks of 'histamine poisoning' involving 1 107 cases were reported to the Centers for Disease Control in the USA.[1] Most of the outbreaks were rather small, involving 5 or fewer individuals per incident. However, in 1973 a large outbreak, which involved 232 individuals, occurred in the USA, after the victims had ingested commercially canned tuna.[5] A reference to an outbreak of histamine food poisoning in South Africa, involving 70 people, was found.[2] Further details of the latter incident could unfortunately

TABLE I.
Fish species which may be associated with scombroid poisoning in the RSA*

Common name	Family	Genus and species
Yellowfin tuna	Scombridae	*Thunnus albacares*
Southern bluefin tuna		*T. thynnus maccoyii*
Big-eye tuna		*T. obesus*
Longfin tuna (albacore)		*T. alalunga*
Skipjack tuna		*Katsuwonas pelamis*
Eastern little tuna (little tunny)		*Euthynnus affinis*
Atlantic bonito		*Sarda sarda*
Striped bonito		*S. orientalis*
Chub mackerel		*Scomber japonicus*
King mackerel		*Scomberomorus commerson*
Saury (Atlantic saury)	Scomberesocidae	*Scomberesox saurus*
Bluefish (elf)	Pomatomidae	*Pomatomus saltatrix*
Dolphin fish, mahi-mahi	Coryphaenidae	*Coryphaena hippurus*
Yellowtail	Carangidae	*Seriola lalandii*
Pilchard (Pacific sardine)	Clupeidae	*Sardinops sagax*
Cape anchovy	Engraulidae	*Engraulis japonicus*

*This table was compiled and adapted from Taylor[2] to reflect the species of importance in southern Africa. To date, the only species that have been associated with scombroid poisoning in the RSA are yellowtail and tuna.

not be obtained.

Between January and April 1990 the Pharmacology and Toxicology Consultation Centre of Tygerberg Hospital and the University of Stellenbosch received enquiries about 10 incidents of food poisoning involving 22 patients with symptoms and signs suggestive of scombroid poisoning. This article describes these cases and their outcome.

Patients and methods

The consultations regarding suspected scombroid poisoning were followed up either by patient interview or by examination of the data from the hospital files of the patients. All the incidents occurred in the Cape Town region, except for 1 case from Kimberley, which involved fish transported from Cape Town. The fish was bought from various outlets and consumed grilled or fried in restaurants or at home.

Fish specimens could only be obtained in 3 incidents. The histamine levels of these specimens were determined by liquid extraction with *n*-butanol followed by diazotisation and spectrophotometric quantitation at 550 nm (Dr J. P. H. Wessels, Fishing Industry Research Institute — personal communication). Microbiological cultures were performed only on the specimens involved in the Kimberley incident.

Results

The symptoms and signs of scombroid poisoning documented in this case series are summarised in Table II. Although the intensity of symptoms and signs differed between individuals, all who ate the toxic fish were affected. In most patients the symptoms and signs appeared within 10 - 30 minutes after ingestion of the fish.

The skin manifestations were the most prominent feature. They appeared within minutes to an hour, and seldom lasted for more than 6 hours. Most patients experienced a hot, blotchy flushing of the skin, resembling an ethanol flush or severe sunburn, with well demarcated borders, especially of the face, neck and upper chest. Pruritus was an infrequent feature. Although some patients experienced a sharp peppery taste, more than 70% of the patients noted nothing unusual about the taste or appearance of the fish. The fish involved in all cases was the Cape yellowtail (*Seriola lalandii*). Most patients were treated with antihistamines and responded well and in the majority the condition

TABLE II.
Scombroid poisoning — symptoms and signs most frequently documented in this series (*N* = 22)

Symptoms and signs	% of patients
Skin manifestations (see text)	82
Diarrhoea; often watery, can appear within 1 - 2 h but usually within 6 - 8 h	77
Palpitations/tachycardia	64
Headache, described as throbbing	46
Nausea, abdominal cramps and discomfort with occasional vomiting	46
Paraesthesia, hypo-aesthesia, often described as a tingling sensation around the mouth, as well as in the tongue and legs; scratchy feeling in the throat	32
Unusual taste, frequently described as peppery or pungent, but sometimes bitter	27
Breathing difficulties/shortness of breath — chiefly in patients with a history of asthma or allergy	23

resolved within 12 - 24 hours. Two individuals with a history of allergy, 1 of whom was also a migraine sufferer, received, in addition to the antihistamines, hydrocortisone and theophylline intravenously. An asthmatic patient required the administration of salbutamol.

Analysis of 3 specimens of fish revealed histamine levels of 25, 72 and 162,5 mg/100 g. The unofficial maximum allowable commercial level in the USA for histamine in fish tissue is 10 mg/100 g.[4]

Microbiological culture of the fish specimens from Kimberley revealed a growth of *Proteus morganii*.

Discussion

Although histamine plays an important role in the pathogenesis of scombroid poisoning, the exact mechanism is still unresolved. A number of factors implicate histamine as one of the major causative agents. These include the similarity between the clinical picture of histamine poisoning and scombrotoxism and the fact that antihistamines rapidly relieve the symptoms of both.[4] In addition, there exists a positive correlation between an increased level of histamine in the spoiled fish and the clinical syndrome of scombroid poisoning. On the other hand, large amounts of histamine can be taken orally without causing effects, since most is converted by intestinal bacteria to inactive *N*-acetyl histamine. The free histamine absorbed is rapidly inacti

vated by *n*-methyltransferase and diamine oxidase as it transverses the intestinal wall or circulates through the liver.[6-9] Furthermore, it is well known that food containing relatively high concentrations of histamine can induce histamine food poisoning in patients on isoniazid treatment, since the drug is a potent inhibitor of diamine oxidase (histaminase).[10-12] It follows therefore that although histamine plays a pivotal role in the pathogenesis of this condition it is probably not the primary toxic 'trigger'. Some authors speculate that, in addition to histamine, the spoiled fish also contains other heat-resistant histamine-like substances or 'scombrotoxins'. These could act as potentiators, either by enhancing the absorption of histamine or by inhibiting its metabolism. It may be that these potentiators could decrease the threshold dose of histamine needed to provoke an adverse reaction in humans when challenged orally.[2,6,13]

The scombrotoxins (including histamine) are heat stable and scombroid poisoning occurs after ingestion of cooked, smoked or canned fish.[3,4]

Fish with a relatively high content of red meat, which turns brown when cooked, contain high concentrations of free histidine in their muscle tissue.[2,4,5,14] When such fish are improperly refrigerated or refrigeration is delayed, bacteria, which contain histidine decarboxylase, convert histidine to histamine.[1,2,6] Enterobacteriaceae, such as *P. morganii* and *Klebsiella pneumoniae*, possessing high histidine decarboxylase activity, are often implicated in scombroid poisoning.[2,4] Since these organisms are not part of the normal enteric and surface marine microflora, it is suggested that post-catch contamination with histamine-producing bacteria may set the chain of events in motion.[2] This may occur during handling of the fish on board the fishing vessel, at the processing plant, in the distribution system or at the level of the user. Microbiological culture of the fish obtained in the Kimberley incident of our series revealed a growth of *P. morganii*.

The extent of dark-meat fish spoilage usually correlates well with histamine levels. Histamine levels in freshly caught fish are less than 1 mg/100 g of fish,[15] but if left at room temperature it can increase rapidly, reaching toxic levels of up to 100 mg histamine/100 g of fish within 12 hours.[16] The US Food and Drug Administration has established 50 mg/100 g of fish to be a hazard level.[1,14,17] The unofficial maximum allowable commercial levels for histamine in fish tissues in the USA is 10 mg/100 mg.[4] The histamine levels obtained in our series were all above the allowable level and 2 of them were above the hazard level.

The diagnosis of scombroid poisoning is generally made on clinical grounds.[1,5,6,18] All the patients in our series presented with a clinical syndrome resembling scombroid poisoning. The onset was rapid. Skin manifestations, especially of the face, neck and trunk; palpitations; headache; and also gastro-intestinal symptoms and signs were the most prominent (Table II). Contrary to reports from elsewhere,[4,5] swelling of the lips and tongue, with blistering, did not occur in our series. Similarly, pruritus and sweating occurred only infrequently. A comparison between our patients and those reported earlier appears in Table III.[4,5,17]

Scombroid poisoning should be recognised and should not be confused with a true seafood allergy.[6] Patients with scombroid poisoning are often misdiagnosed as having a food allergy and inappropriately instructed to refrain from eating seafood.[1,18] Factors which support the diagnosis of scombroid poisoning are the following: the high number of individuals afflicted in a group outbreak; the consumption of a common species of fish by everybody involved in an incident, and also a common species implicated in different outbreaks; the detection of high levels of histamine in the toxic fish; and the lack of a history of allergies. The differential diagnoses include food allergy, bacterial food poisoning, disulfiram reaction, Chinese restaurant syndrome, ciguatoxin poisoning, carcinoid syndrome, phaeochromocytoma and Zollinger-Ellison syndrome.[19]

Scombroid poisoning is a relatively mild, self-limiting condition, but it can pose a serious risk to patients suffering from allergic conditions, the elderly, those suffering from cardiac disease, and also patients on isoniazid therapy.

The treatment of the condition is symptomatic and supportive.[6] The majority of patients in our series were treated with antihistamines with good results. The classic antihistamines (H_1-receptor blockers, e.g. promethazine or diphenhydramine) are the drugs of choice. A recent report[20] described 4 patients who showed rapid relief of symptoms with the intravenous administration of cimetidine (H_2-receptor blocker). In the atopic patient, where bronchospasm or other severe histamine reactions may occur, the use of ß-adrenergic agonists, theophylline and even corticosteroids should be considered.

Care should be taken not to consume fish that has a peppery or unusual taste, a 'honeycomb' appearance of the flesh or has been subjected to suboptimal handling and storage conditions.[14,21] Unfortunately, the physical appearance of spoiled fish may be unremarkable.

The apparent non-reporting of scombroid poisoning in South Africa may be due to misdiagnosis, lack of awareness on the part of clinicians, and also the self-limiting nature of the condition. Health workers are strongly urged to alert health authorities when encountering suspected cases of scombroid poisoning. This will facilitate identification of the source of the contaminated fish, thereby limiting the incidence of poisoning. Since yellowtail at present appears to be the major species involved, more attention should be given to the handling and storage of this fish. Customary displays of fish on ice may not offer sufficient protection.

TABLE III.
Scombroid poisoning — a comparison of clinical profiles in our series and those reported from elsewhere

Clinical Profile	% of patients			
	Our series (*N* = 22)	Merson *et al.*[5] (*N* = 232)	Kow-Tong and Malison[17] (*N* = 115)	Russell and Maretic[4] (*N* = 17)
Skin manifestations	82	46	62	94
Diarrhoea	77	55	13	59
Palpitations/tachycardia	64	*	30	60
Headache	46	44	51	63
Nausea, abdominal cramps, vomiting	46	86	51	41
Paraesthesia, hypo-aesthesia	32	*	35	*
Abnormal taste	27	63	*	100
Breathing difficulties	23	*	*	*

*Symptoms and signs not mentioned in the case studies from elsewhere.

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