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FISH INTOXICATION

Notes on Ciguatera,
Its mode of action
And a suggested

THERAPY

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JUN 1 1963

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The South Pacific Commission

The South Pacific Commission is an advisory and consultative body set up in 1947 by the six Governments then responsible for the administration of island territories in the South Pacific region (Australia, France, the Netherlands, New Zealand, the United Kingdom and the United States of America). Participation by the Netherlands Government ceased at the end of 1962.

The Commission's purpose is to advise the participating Governments on ways of improving the well-being of the people of the Pacific island territories. It is concerned with health, economic and social matters. Its headquarters are at Noumea, New Caledonia.

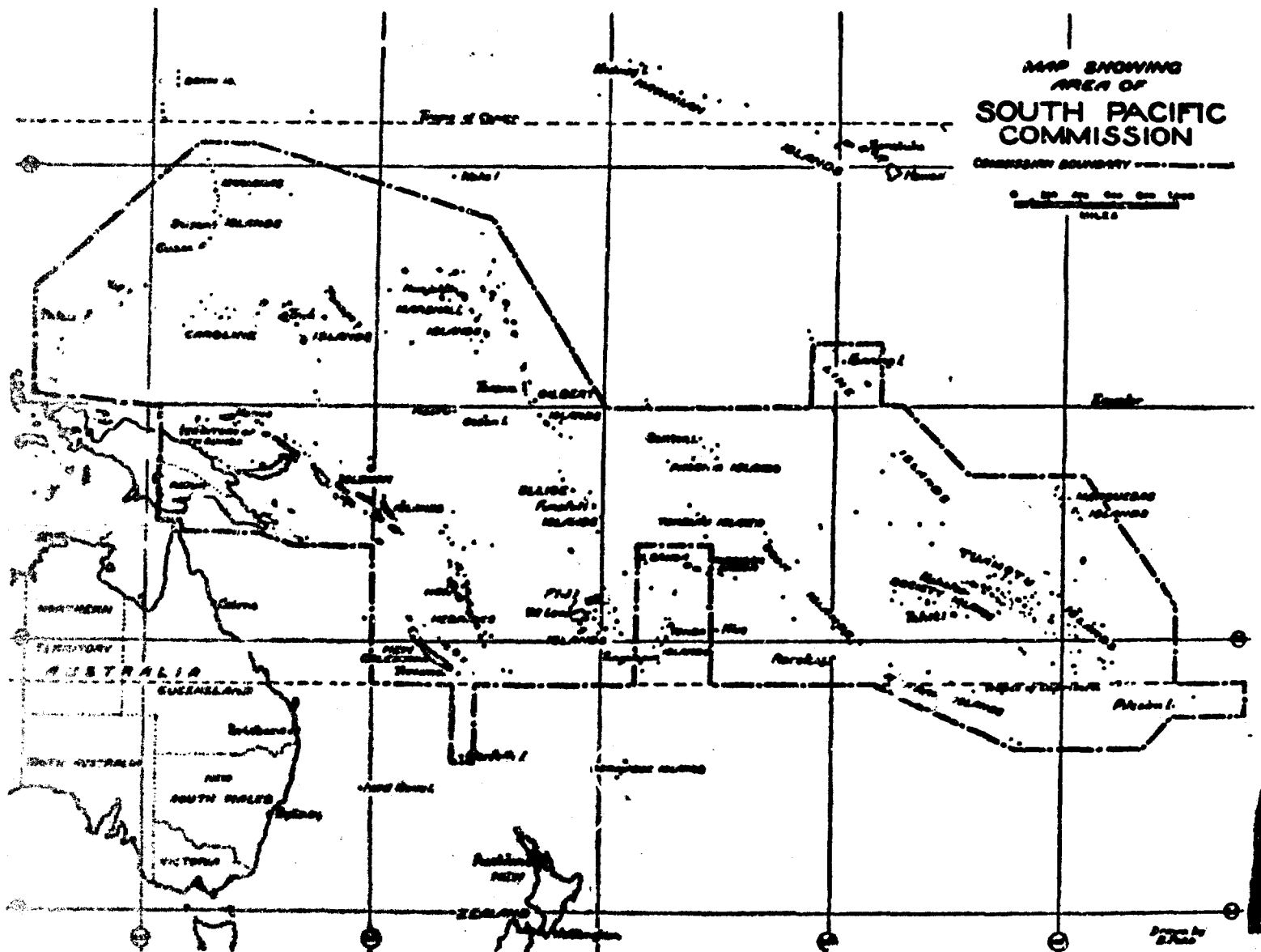
The Commission consists of not more than ten Commissioners, two from each Government. It normally holds one session each year. There are two auxiliary bodies, the Research Council and the South Pacific Conference.

There is a Research Council meeting normally once a year. This may be either a meeting of the full Council, or of one or other of its three main sections, specialising in the fields of health, economic development and social development. Members of the Research Council are appointed by the

Commission. They are selected for their special knowledge of the questions with which the Commission is concerned, and the problems of the territories in these fields. The chief function of the Research Council is to advise the Commission on what investigations are necessary and on the work programme. Arrangements to carry out those that are approved are the responsibility of the Secretary-General and other principal officers.

The South Pacific Conference, which meets at intervals not exceeding three years, consists of delegates from the local inhabitants of the territories, who may be accompanied by advisers. The first Conference was held in Fiji in April, 1950. The second Conference was held at Commission headquarters in April, 1953, the third in Fiji in April-May, 1956, the fourth in New Britain in April-May, 1959, and the fifth in Pago Pago, American Samoa, in July, 1962.

The principal officers of the Commission are: Secretary-General, Mr. W. D. Forsyth; Executive Officer for Social Development, Dr. Richard Seddon; Executive Officer for Economic Development, Dr. Jacques Barreau; Executive Officer for Health, Dr. Guy Lolson. The powers and functions of the Deputy Chairman, Research Council, are exercised by the Secretary-General.



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F I S H I N T O X I C A T I O N

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and a suggested T H E R A P Y

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Noumea, New Caledonia
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I N T R O D U C T I O N

"In New Caledonia, some apprehensive people no longer dare to eat fish".

This statement was made nearly a century ago by the explorer J. Garnier and it is still true of New Caledonia to-day. This fact explains, partly, why fish is imported from nearby Australia, or even from France, into a country with a lagoon abounding in succulent species of fish.

Experiments being carried out currently by the South Pacific Commission indicate that about 5% only of the fish reputed to be toxic are in fact so. The proportion is undoubtedly even lower in respect of the other species of fish. However, the amount of fish caught, and consumed, is such that large numbers of the population are exposed to the risk. Fish toxicity has, therefore, become an economic problem (reluctance to open a tinning factory) and a health problem (reluctance of mothers to feed fish to their babies during the weaning period, thus depriving them of essential - and cheap - nutritional elements).

Replies to a questionnaire sent out by the South Pacific Commission indicate that fish toxicity is recorded in practically every island in the region; it has, therefore, become also a therapeutic problem - for the physicians who must minister to its many victims.

"The islanders attribute these illnesses to evil spirits who will conceal themselves in the bodies of fish to torment them", writes J. Garnier in his "Voyage autour du monde", Océanie, p. 179, 1871. The medicine men obviously employed esoteric methods to dispel such evil spirits, but they also gave their patients various concoctions based on local medicinal plants. The credit of these medicine men has waned considerably since the arrival of European physicians in increasing numbers and the growth of efficient Health Services. In local villages, the younger generations are gradually forgetting the traditional pharmacological lore, to such an extent that research workers, be they botanists or medical officers, attempting to gather information on the therapeutic value of various plants have great difficulty in sorting out facts from legends.

One certain fact, however, is that there are so many plants reputed to be effective in the treatment of fish poisoning that one tends to become doubtful

about their virtue. This means also that western medicine has not yet discovered the perfect cure for the disorders caused by toxic fish, probably because the toxin has not yet been identified chemically and because the pathogenesis of the disease is still ill-defined.

In New Caledonia, for example, the plants used by Europeans and Melanesians alike serve mostly to alleviate certain symptoms such as diarrhoea or vomiting, or again to increase diuresis. Taken orally, or rubbed onto the skin, some plants are said to have anti-pruritic properties. Leaves, flowers, fruits, bark, seeds or roots are used to make macerations or decoctions which are taken at the dose of 1 to 3 litres daily for several days. Let us quote, inter alia, Morinda citrifolia L., (tonic and anti-diarrhoeal), Thespesia populnea L., (depurative), Sophora tomentosa L., (emeto-cathartic), Nothopanax guilfoylei (Cogn. & March.) Mer., (tonic and anti-pruritic), Erythrina fusca Lour., var. fastigiata Guillaumin (sedative, purgative and diuretic), Duboisia myoporoides R. Br. (narcotic), and, the most popular, Messerschmidia argentea Johnston (anti-pruritic). Samples of the latter two have been sent to the University of Iowa, where Professor William H. Ogell has kindly agreed to carry out gratuitously, for the South Pacific Commission, a number of analyses to determine the presence of pharmacological substances which act on the nervous system.

The treatments prescribed by physicians are also based on symptomatology; each one, however, has his own favourites. In Bourail (New Caledonia), Dr. Boutin (personal communication) asks the people to keep in their refrigerator a small piece of the fish they are ready to cook; if a case of fish poisoning occurs, he prepares an homeopathic dilution with the raw piece of the incriminated fish and administers it per os to the patient. We shall gloss over the favourable results claimed by acupuncture practitioners to mention only those published in the more conformist press. At Fanning (Central Pacific), Dr. S.G. Ross prescribed nux vomica and chloroform water after a stomach-washing and a dose of castor oil (Medical Journal of Australia, 17 January, 1948, p. 63). At Noumea (New Caledonia), Dr. Vaillant treats his patients with anti-histamins, delta-cortisone and heart tonics (Bulletin de la Société de Pathologie Exotique, 54, 1961). In the same issue, Dr. Blin writes that anti-histamins have no effect: he advocates symptomatic treatment with the addition of cortisone; in respect of Messerschmidia argentea, he believes that the virtue of an infusion of this plant of the Boraginaceae family depends mainly on the seriousness of the symptoms to be treated. In 1962, in the Bulletin de l'Association Médicale de Nouvelle-Calédonie and in the Bulletin de l'Institut Océanographique de Monaco, No. 1240, Doctors Boudier and Cavallo published a treatment combining intestinal disinfectants, anti-spasmodics and rehydration which cured the digestive disorders although the analgesics which they also prescribed had no effect on pruritus, dysesthesia and paresthesia. It was sometimes necessary to use morphine. These authors mention

the beneficial, although variable, effect of Messerchmidia argentea. Finally, they indicate the promising results of their first experiments with vitamin B6 which, administered in intramuscular or intravenous injections at a dosage of 250 mg., relieves the sensory disorders for 3 to 5 hours. Several of their colleagues told us, however, that their own experience with vitamin B6 did not match the results claimed by these authors. In the New Hebrides, Dr. de Carfort (personal communication) obtains satisfactory results with a treatment consisting of calcium injected intravenously (10 to 20 ml.) and sparteine administered subcutaneously (0.50 g.).

It seems, therefore, that there is ample scope for further therapeutic experimentation and, for this reason, we have sought permission from Drs. Banner, Shaw, Alender and Helfrich to publish their work on the treatment of Ciguatera with neostigmine. We are grateful to them for this renewed proof of their trust in us and, once again, are pleased to acknowledge the excellent way in which the Laboratory of Marine Biology of the University of Hawaii and the South Pacific Commission co-operate in research on fish toxicity, a problem of vital importance in all the territories in the region.

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FISH INTOXICATION:

NOTES ON CIGUATERA, ITS MODE OF ACTION AND A SUGGESTED THERAPY^{1,2}

By

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That certain fishes may be toxic to eat has long been well known throughout the tropical Pacific. At least three different types of fish poisoning have been established by laboratory studies :

- (i) Tetraodon poisoning, which is caused by eating the flesh, or more commonly, the visceral organs of various species of puffer fishes (also called balloonfish, swellfish, toadfish, or globefish) and their relatives. The toxin, which is water soluble, has been isolated; it is evidently endogenous and is found in these fish in the tropical Pacific, Atlantic and Indian Ocean regions (Yudkin, 1944; Halstead, 1959).
- (ii) Scombroid poisoning, which is caused by eating the flesh of tunas and mackerel-like fish which have been subject to pre-putrescent bacterial action. The toxin or toxins, histamine-like in action, are produced by the action of Proteus morganii on naturally occurring substances in fish flesh, and their action is not detectable by the usual smell of decomposition (Kawabata, et. al., 1956, Kimata in Borgstrom, 1961).

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1. Contribution No. 183, Hawaii Marine Laboratory. The studies reported here were supported in part by the following grants: U.S. Public Health Service Grants EF-00216, EF-00224; Atomic Energy Commission Contract AT(04-3)-235; Office of Naval Research Contract Nonr-2289(00) NR 107 405; National Institutes of Health Contract SA-43-ph-3741.
 2. This paper has been prepared at the suggestion of the South Pacific Commission for the use of medical personnel in the tropical Pacific; some of the reported findings have been published in previous papers, and those findings reported here for the first time will be covered more extensively by other papers now in preparation.
 3. Albert H. Banner, Charles B. Alender and Philip Helfrich, Hawaii Marine Laboratory, University of Hawaii, Honolulu 14, Hawaii; Spencer W. Shaw previously with the U.S. Naval Hospital, Guam, and now at Doctors' Hospital, Seattle, Washington.

- (iii) Ciguatera, which is caused by eating the flesh of a variety of large carnivorous and small herbivorous fish from restricted areas on coral reefs in the Pacific and Indian Oceans, and the Caribbean Sea. The toxin causing this disease can be extracted from the flesh with alcohol and other organic solvents (Banner and Boroughs, 1958); it is the topic of the discussion below.

Many species of fish have been implicated as causing ciguatera; Halstead (1957) claims that more than 325 species of marine teleost fishes have been reported as causing gastrointestinal and neurological symptoms typical of this disease. Those species most frequently implicated are among the snappers (Lutjanidae), groupers (Serranidae), Pompano or jack (Carangidae), barracuda (Syphraenidae), moray eels (Muraenidae), and surgeonfishes (Acanthuridae). Many other fishes have been said to have caused ciguatera, from sharks to some of the plectognath fishes (boxfish, filefish, triggerfish). Little scientific investigation has been carried out on the nature of the toxin in these scattered species, but it is possible that all of these may carry the same toxin in toxic areas.

Reports in the literature and in our files on cases of intoxications resembling ciguatera come from almost all parts of the tropical Pacific. Among the major island groups in the Pacific which have reported cases of ciguatera are the following: Ryukyu, Mariana, Caroline, Marshall, Gilbert, Ellice, Fiji, Samoan, Phoenix, Society, Tuamotu, Marquesas, Line, Hawaiian, and Tonga Islands, as well as New Caledonia, the New Hebrides, the Bismarck Archipelago, and parts of New Guinea and tropical Australia. In some archipelagoes, as in the Hawaiian Islands, cases are rare.

Within an archipelago the toxicity may be confined to certain islands. Thus in the Gilbert Islands, Mrs. Jane Cooper reports (manuscript in preparation for publication) that 10 of the islands report fish causing ciguatera, while 6 have no such fish. Furthermore, she has found that the Gilbertese know about the toxic areas through extensive experience, and the toxic areas are confined to limited sections of the reef about an atoll. These sections are always on the lee side of the islands (western and southwestern portions in the Gilberts).

The symptoms of ciguatera are quite varied, and the clinical picture is quite bizarre; not all of the patients display the same syndrome, even among a group that has all eaten of the same fish. A list of symptoms has been compiled by one of us (Helfrich, 1960) from the numerous case reports and published accounts of ciguatera. The first symptoms are usually experienced within about 3 hours after ingestion and consist of nausea, and vomiting, followed by tingling and numbness about the lips, tongue and throat. These symptoms may be followed by abdominal pain and cramps, diarrhoea, arthralgia, muscular weakness, incoordination, numbness and tingling of the extremities, malaise, chills, low-grade fever, and prostration. Hypotension, profuse sweating, dyspnea, restlessness, insomnia,

headache, intermittent dizziness, dilation of the pupils, ptosis, divergent strabismus with diplopia, reduced vision, dryness of the mouth, a metallic taste, and myalgia (particularly severe in the back and thighs) also occur. Hyperesthesia, urinary retention and diminished to absent knee and ankle reflexes have been reported. Patients often experience dysesthesia that consists of a confusion of temperature sensation; when touching a cold object, the patient reports that it gives the sensation of burning, tingling, or "dry ice", and hot objects feel cold. When tap water is swallowed, it often gives the sensation of being carbonated. Muscular asthenia, particularly of the lower limbs, often results in the patient having difficulty in walking and particularly in climbing stairs. Pruritus has been reported, and it is often localized in the palms of the hands and soles of the feet, but in a few cases is more generalized. According to Boudier and Cavallo (1962) this symptom occurs in less than 30% of the cases and therefore it does not justify calling it "la gratte" (= the itch) which is the common name given to ciguatera in New Caledonia. In severe cases of ciguatera, shock, convulsions, muscular paralysis, and death may occur.

It appears as though the body does not rapidly neutralize or eliminate ciguatera toxin, for characteristically, the recovery period is quite prolonged. Typically, most of the gastrointestinal symptoms subside in 24 hours; however, muscular weakness, tingling, and numbness may last from 4 to 7 days or longer. During the recovery phase some patients report a vague neuralgic pain about the teeth, giving the sensation that their teeth are falling out.

An attack of ciguatera does not impart immunity; on the contrary, patients who have been poisoned previously report a mild recurrence of symptoms after eating a slightly toxic fish, while others who have never been poisoned experience no symptoms when eating the same fish.

Unfortunately, adequate scientific studies have not been made to determine whether the great number of species implicated in outbreaks of ciguatera in widely scattered areas all bear the same toxin. Most of the work upon the biological and chemical nature of the toxin has concentrated on the red snapper, Lutjanus bohar (Forskål) from the Line Islands (Banner *et al.*, 1960; Hessel *et al.*, 1960; Hessel, 1961). Because parallel chemical extractions through a series of steps produce a toxin which has reaction in mice similar to that produced by the toxin from L. bohar, it is suspected that the following species of fish from the toxic areas in the Line Islands carry a toxin similar to, or identical with, that of L. bohar:

Gymnothorax javanicus (Bleeker) (Moray eel)
Garanx ignobilis (Forskål) (Ulua, Jack, Pompano)
Epinephelus fuscoguttatus (Forskål) (Grouper, Sea bass)
Lutjanus gibbus (Forskål) (Red Snapper)
monostigmus (Cuvier and Valenciennes) (Snapper)
vaigiensis (Quoy and Gaimard) (Snapper)

Lethrinus miniatus (Forster) Bloch and Schneider
 (Scavenger, Gray Snapper, Sweetlips)
Acanthurus triostegus (Street) (Surgeon Fish)
Acanthurus xanthopterus (Cuvier and Valenciennes)
 (Surgeon Fish)
Ctenochaetus striatus (Quoy and Gaimard) (Surgeon
 Fish)
Sphyræna barracuda (Walbaum) (Barracuda, Barracouti)

On the basis of similarity of environment and similarity of symptoms produced in either humans or test animals, it is suspected that other fish of the toxic reef complex where the above fish are found will also be found to bear the same toxin. These fish include other groupers, snappers, parrotfish, and wrasses.

Further, it is not known if the toxin found in the ciguateric fish listed above is the same from archipelago to archipelago. Tests reported below have indicated that there is no difference in solubilities or pharmacological action between the toxins from fish in the Line Islands and the Marianas. Case histories, gathered in various Pacific archipelagoes, indicate a parallel series of symptoms no matter where fish poisoning occurs although the syndrome varies considerably among individuals. From this it may be presumed that if the toxins are not the same, they probably are similar. However, Dr. E. Massal, Director, Institut de Recherches Médicales de la Polynésie Française, reports, "In Tahiti, the persons afflicted with ciguatera complain - after the transitory gastro-intestinal episode - more of superficial paresthesia and weakness in the limbs than of the intense itching so commonly observed in New Caledonia patients and known as la gratte." Dr. Massal suggests that the difference in symptoms may be due to a difference in the nature of the toxin harbored by the fish in the two areas.

There are also a series of fish and invertebrates reportedly toxic to eat which are suspected, on the basis of either environment or symptomatology, not to carry the same toxin. Among the fish would be those causing hallucinations, such as the mullet from Hawaii, and the "dream fish" (Kyphosus) from Norfolk Island, (Helfrich and Banner, 1960), the toxic sardine or herring from Fiji, New Caledonia and possibly elsewhere, Clupea venenosa, so far unstudied, and the liver of certain sharks (Lonie, 1950). Almost nothing is known about the invertebrates: some snails, as the turban and top shells (Turbo and Trochus) may also carry the toxin causing a ciguatera-like condition, but have not been studied; others, as the toxic crabs from Tonga, the sea slugs whose salivary glands are reportedly lethal, in Samoa and Tonga, have not been investigated.

This report, then, concerns itself specifically with the toxin that is found either in the red snapper, Lutjanus bohar, from the Line Islands, or with the barracuda, Sphyræna barracuda, from the Marianas; the authors believe,

however, that the general conclusions may apply to a wide range of fish from many localities.

General Observations on the Nature of the Toxin

As a service to medical personnel in the South Pacific, the following observations, based on laboratory and field studies and reported in previous publications, here are summarized (see Arcisz, 1950; Bartsch and McFarren, 1962; Banner and Boroughs, 1958; Banner et al., 1960; Helfrich, 1960, 1961; Banner, 1961a, 1961b; Hessel et al., 1960):

1. The toxin is not a product of bacterial action or putrescence, and occurs in fish fresh from the sea.
2. The toxin is thermostable, and may be subjected to temperatures up to 100°C. for 72 hours; correspondingly, fish stored at temperatures below 0°C. for 36 months show no appreciable loss of toxicity.
3. No techniques in preparation of the toxic fish, as immediate evisceration, skinning, or bleeding upon capture will destroy the toxicity of the fish.
4. As the toxin is not initially water soluble, it cannot be removed from the flesh by washing or leaching in water as is sometimes done with the puffer fish.
5. No method of culinary preparation, as by baking, boiling, steaming, frying or roasting, appears to decrease the toxicity of a fish.
6. In general, the larger fish from a toxic area are more dangerous than the smaller fish of the same species; for example, few of the Lutjanus bohar under 50 cm. (18 inches) long from the toxic area at Palmyra Atoll would cause toxic symptoms when fed to mongooses (the laboratory test animal). On the other hand, surgeon fish which reach full size at the length of 15 or 20 cm. (six or eight inches) (such as Ctenochaetus striatus) may cause severe symptoms.
7. Within an individual fish, the flesh is less toxic than the viscera, and within the viscera, the liver and the testes are found to be the most toxic.
8. The toxin may be detected by feeding the fish flesh or viscera to cats or mongooses, both of which develop lack of coordination and inability to stand, and with highly toxic fish, will die within 48 hours; the cat, but not the mongoose, may vomit. Dogs and pigs are also reported to be susceptible, and conflicting reports exist on the susceptibility of chickens to ciguatera toxin.

9. In none of our observations could we detect difference in color or configuration between toxic and nontoxic fish of the same species, except for size as noted above.
10. All reports on distribution of the toxic fish about islands have indicated them to be often confined to narrow and geographically discrete areas, as near the mouth of a channel to a lagoon, or the lee side of a small island; studies now in progress at Palmyra and Christmas atolls tend to confirm this distribution.
11. As yet, studies at Palmyra and Christmas atolls have not positively shown any seasonal differences in toxicity, although a complete series for a full year has not been processed; however, unverified reports from Fiji have indicated a strong seasonality in the toxicity there.
12. Public Health statistics and our studies indicate that over a period of years toxicity may build up around an island, and then slowly decline; on certain islands, on the other hand, some species of fish have remained toxic for almost two centuries (Capt. Cook reported poisoning in 1776 from the New Hebrides) (Anderson, 1776).
13. None of the "tests" for toxicity reported from various Pacific Islands appear to be reliable specifically:
 - (a) The silver coin test: At the Hawaii Marine Laboratory a silver coin, previously cleaned with acid, was boiled for a half hour with the flesh of a nontoxic fish, and a similarly cleaned coin with fish of high toxicity, as established by feeding tests; at the conclusion of the experiment no differences between the two coins in either sheen or color were noted.
 - (b) The fly test: Two pieces of flesh, one highly toxic and one nontoxic, were exposed to the common flies of Honolulu, and the number of flies resting on either piece was recorded every 30 seconds for 15 minutes; there was no statistical difference between the number alighting on the two pieces. Moreover, flies, cockroaches, and dermestid beetles were raised in laboratory culture on either putrescent or dried fish flesh of established high toxicity.
 - (c) The ant test: Similarly to the fly test, two pieces of flesh were exposed to the common ants and no detectable difference was found in the attractivity of toxic and nontoxic flesh.
 - (d) The copper test: A number of pieces of copper wire were cleaned

in acid and cooked with toxic fish and controls in both water and vegetable cooking oil. The fish used was Lutjanus bohar; as a test sample, a specimen from Palmyra Atoll of established high toxicity was chosen, which was contrasted to two nontoxic specimens, one from Palmyra and one from the Manila (Philippines) fish market; as an additional control, wires were "cooked" in the water and cooking oil without fish. In the fish samples the wire was placed above and below the sample of fish; the upper wires were partially exposed to the air in the process of cooking. After 45 minutes of cooking at a moderate heat, it was found that the upper wires in the toxic and in the control specimens had blackened, but the wires under the fish and in the control without fish remained unchanged.

14. Extensive studies have shown that there is no correlation between radioisotopic contamination in the fish flesh (radioactivity) and the toxicity of the specimen (Helfrich, 1960).
15. The cause of the toxicity in the fish is not known, although many hypotheses have been advanced to account for its occurrence, especially in respect to its changing patterns in space and time. Thus, dumped war-surplus materials, the rise of balolo worms, toxic berries from land plants drifting to sea, the "blooming of the coral plants" - all have been suggested as the source of ciguatera toxin. The most coherent and promising hypothesis is that of Randall (1958) who suggested that the toxin originated in certain algae and was passed virtually unchanged through the food chain of small herbivorous fish to the large carnivores, like the groupers and snappers. Experimental work at this laboratory has shown that toxicity in fish can be induced through diet, confirming the basic premise of this hypothesis (Helfrich and Banner, in press).

Notes on the Pharmacology of Ciguatera Toxin

An initial study on the pharmacology of ciguatera toxin by one of us (Alender) in the laboratory of Dr. Paul Saunders, Department of Pharmacology, University of Southern California, was upon rabbits (anaesthetized with either nembutal¹ or urethane²) which were injected with semi-purified toxin (for technique of purification see Banner et al., 1960). On intraperitoneal injection there was an initial increase in respiratory rate, followed by a decrease to below normal; in some cases there was a respiratory arrest, but artificial respiration could prolong the life of the test animal. Concurrently with the respiratory depression there was a fall in blood pressure; electrocardiographic records indicated cardiac changes were minimal. On intravenous injection, there was an immediate decrease in the blood pressure with a simultaneous increase in respiratory rate and depth; subsequently, the blood pressure increased and the

1. Sodium⁵-ethyl-5 (1-methylbutyl)-barbiturate, $C_{11}H_{17}N_2O_3Na$.
2. Ethyl carbamate, $NH_2.CO.CO_2C_2H_5$.

respiration slowed and became irregular (the dosage used was not lethal). Temporary changes were noted in the electrocardiograph, correlated with the initial fall in blood pressure, with a displacement of the ST segment, but a normal picture was regained when the blood pressure increased to near normal.

In the same laboratory the effects of the toxin upon neuromuscular transmission were studied upon a guinea pig phrenic nerve-diaphragm preparation. Here it was found that if the bathing solution contained small amounts of the toxin (see below), there was an immediate impedance of stimulation of the muscle through the nerve fiber, while direct stimulation of the muscle continued to elicit full response.

In a second preparation, a toad sciatic nerve-sartorius muscle preparation was tested using a semi-purified extract of ciguatera toxin in a solution of 1 mg./cc of 2% polyvinylpyrrolidinone (emulsifying agent) in Frog Ringer's solution. Within 35 minutes after the preparation was in contact with the toxin, normal twitch and tetanus by nerve stimulation were lost, although the muscle retained its contractility when stimulated directly.

Therapy for Ciguatera

Most of the treatments for ciguatera are either native herbal remedies which have not been investigated (see Loison, 1955), or drugs for symptomatic relief, or general palliatives (see Halstead, 1959). Recently, Boudier and Cavallo (1962) in Nouméa published on a new remedy based on the use of vitamin B₆ in which they suggested that the symptoms of ciguatera were similar to B₆ avitaminosis; they reported success in treatment with the vitamin. This method of treatment has not been investigated by personnel associated with this project.

However, in 1961, when only preliminary experiments on the pharmacology of the toxin were being conducted at the Hawaii Marine Laboratory, one of the authors (Shaw) was called to treat a potentially fatal case of fish poisoning on Guam. Because of the severity of the patient's condition and the general lack of information and experience in handling ciguatera patients, Dr. Shaw telephoned the group doing research on ciguatera at the Hawaii Marine Laboratory. Dr. Helfrich informed Dr. Shaw that little was known of the mode of action of the toxin, but that Mr. Alender had noted that the toxin in isolated preparations would produce a blockage at the neuromuscular junction but that the exact nature of the block had not been ascertained. On the basis of this information, Dr. Shaw, in consultation with Dr. R.W. Schwab, Massachusetts General Hospital, and Drs. Lt. Kurland and S. Lessel, neurologists of the National Institute of Neurological Diseases and Blindness, National Institutes of Health, Washington, D.C., who happened to be on Guam at the time, decided to try an anticholinergic drug.

Case History 1

A Carolinian female, age 19, was one of two persons stricken with ciguatera after a meal on a portion of a 57-lb. barracuda (tentatively identified from photographs and other information as Sphyraena barracuda). Within twelve hours after the meal both individuals developed nausea, numbness and tingling of the skin of the face and extremities, and weakness with lack of coordination of the arms and legs. Both reported to the U.S. Naval Hospital, Guam. Both were given 2 grams of calcium gluconate¹ intravenously, and the second patient, a male of 42 years, was given intravenous fluids and chlorpromazine² intramuscularly. Both patients had what appeared to be an uneventful recovery, the female being discharged from the hospital in two days, the male in three days after the meal.

The male continued his recovery, but the day after discharge, the third day after the barracuda was eaten, the female was found in an acute relapse, ataxic with great weakness in her left leg; further, she appeared unable to respond to questioning beyond a halting, "I - can't - talk". About 72 hours after the fish meal, she was re-admitted to the hospital.

During the evening and night after re-admission she was given intravenous fluids; by the following morning she was semi-comatose, responding to questioning with only a slow rolling of the head; she was unable to sit and her muscular system was limp with loss of all deep tendon reflexes, absent abdominal reflexes and bilateral extensor plantar responses. A lumbar puncture was performed at this time and again 72 hours later, both of which showed normal pressures, cell count, sugar and protein content.

On noon of that day the patient was given continuous intravenous hydrocortisone³, 100 mg. during the first hour and 50 mg. an hour for the next two. The patient responded in two hours with return to consciousness and a return of the deep tendon reflexes. However, when the dosage was reduced the patient relapsed. On the next day she was in a coma again and did not respond to dosages of 10 mg. of hydrocortisone; again she was given 100 mg. of the drug in one hour and 50 mg. in the next hour, and again she regained consciousness and power of movement. She was then administered 50 - 75 mg. of hydrocortisone every 4 hours, but in spite of the treatment she relapsed into a coma.

On the following day at 1300 (1:00 p.m.), the sixth day after the meal on the fish, she was given 12.5 mg. of chlorpromazine intravenously, which immediately caused further loss in conscious level and depression of respiration. Continued administration of 25 mg. of hydrocortisone every 4 hours brought no response. At this point Dr. Shaw called Dr. Helfrich.

At 1900 (7:00 p.m.) 0.6 mg. of atropine sulfate⁴ was administered intra-

1. $\text{Ca}/\text{HO}.\text{CH}_2(\text{CH}.\text{OH})_4\text{COO}/2.\text{H}_2\text{O}$

2. 2-Chloro-10-(3-dimethylaminopropyl)-phenothiazine, $\text{C}_{17}\text{H}_{19}\text{ClN}_2\text{S}$

3. Hydrocortisone 21-sodium succinate, $\text{C}_{25}\text{H}_{33}\text{NaO}_8$

4. $(\text{C}_{17}\text{H}_{23}\text{NO}_3)_2.\text{H}_2\text{SO}_4.\text{H}_2\text{O}$

venously in a single dose; this brought immediate alertness to the patient, but within 15 minutes she again was sleepy. Within a few minutes endrophonium bromide (Tensilon)¹ was administered intravenously in 2 mgm. doses every 2 to 3 minutes over 10 to 15 minutes and the patient showed slight improvement. Five mg. of the drug was then given in a single dose. Within one minute the patient was able to sit, talk coherently, and showed flexor plantar responses bilaterally. However, within six minutes the plantar responses changed from flexor to extensor, and the patient showed weakness and a slowness of speech. The 5 mg. dose was repeated and again in 8 minutes she was lapsing into a semi-comatose state.

At this point, she was placed on neostigmine methylsulfate², 0.5 mg. intramuscularly every hour, and the hydrocortisone therapy was cut to 10 mg. every 4 hours.

By the next morning the patient was awake and alert, showed no facial weakness, had good strength bilaterally and bilateral flexor plantar response. During the next day she continued to improve except for one episode of diarrhoea which responded to withdrawal of the neostigmine for two hours; subsequently, she was changed to oral administration of 15 mg. of neostigmine bromide³ every two hours.

From this point on she rapidly improved; neostigmine therapy was discontinued 36 hours after initiation, and hydrocortisone was further reduced, changed to oral prednisone⁴ at 2.5 mg. daily for 4 days and then discontinued.

On the fourteenth day after the original meal she was discharged, but for some weeks afterwards she felt she was "slow", and at school her typing speed dropped from a prepoisoning speed of 50 - 60 words to 10 - 15 words a minute. Ten months after the attack, she had no complaints except for occasional weakness in her left arm and leg that was associated with fatigue or "bad weather".

Laboratory studies associated with Case 1

To establish firmly that the barracuda eaten by Dr. Shaw's patient was toxic and that the toxin was similar in chemical nature and pharmacological action to that found in Lutjanus bohar from the Line Islands, a 849.5 gram sample of the flesh of the barracuda was sent to the Hawaii Marine Laboratory for assay. A similar sample was sent to Dr. Bruce Halstead, of World Life Research Institute, but his findings have not been reported upon as yet. The sample, which had been preserved in a frozen condition, had a wholesome color, texture and odor. The analysis was conducted by Mr. Alender⁵.

1. N-Ethyl-3-(m-hydroxyphenyl)-N, N-dimethylammonium bromide, $C_{10}H_{16}NO.Br$.
2. (m.-hydroxyphenyl) trimethylammonium methylsulfate dimethylcarbamate, $C_{13}H_{22}N_2O_6S$
3. (m-hydroxyphenyl)trimethylammonium bromide dimethylcarbamate, $C_{12}H_{19}BrN_2O_2$
4. 17 α , 21-Dihydroxy-1, 4-pregnadiene-3, 11, 20-trione, $C_{21}H_{26}O_5$
5. The authors wish to thank Dr. Finley E. Russel, Laboratory of Neurological Research, Loma Linda University, California, for his help and the use of his laboratory and apparatus in this phase of the investigation.

Following standard extraction procedure (Banner et al., 1960) the flesh was dried, extracted with hot ethanol; the extract was then washed with petroleum ether and re-extracted with diethyl ether. The yield from the diethyl ether was 0.0984 g. (0.011%) of oily viscous material. This extract was made up to 5.65 ml. in Ringer's solution with 2% polyvinylpyrrolidinone (PVP), 1 ml. of the solution therefore equals to the extract from 150 g. of the original sample.

Mouse bioassay: Albino mice (closed colony Carworth Farms Webster strain) weighing 18 - 22 g. were injected intraperitoneally at the levels of 0.50, 0.25, 0.10 ml. of the solution per 20 g. mouse, 2 mice per level, and the time to death was recorded. The results are shown in Table 1.

Table I

Results of Intraperitoneal Injection with Barracuda Extract

D O S E		T I M E T O D E A T H	
ml per mouse	gamma per gram	Minutes	
0.50	435	6.0	7.5
0.25	217	9.5	11.0
0.10	87	20.2	25.5

Toad sciatic nerve-sartorius preparation: This preparation was treated with the extract in Frog Ringer's solution at a concentration of 174 g. per ml. Electrical stimulations, both single and tetanizing, were applied to the nerve every five minutes, and the resultant contractions were recorded on a smoked drum kymograph with a weighted isotonic lever. The results are recorded in Table 2.

Table 2

Reaction in a Sciatic Nerve Sartorius Preparation
When Bathed with Barracuda Extract

Time of exposure to toxin (Minutes)	Contraction (Single shock)	Contraction (Tetanizing)
0	Full	Full
5	None	1/3 normal
10	None	1/3 normal
15	None	None
20	None	None
25	None	None

Direct stimulation of the muscle after the 25-minute test period produced normal contractions, and the action potential in the nerve was normal.

Guinea pig phrenic nerve-diaphragm preparation: Four preparations were studied with the barracuda extract at concentrations of 200 μ g., 40 μ g., 10 μ g. and 4 μ g. per ml. of bath. In no case were directly elicited contractions interfered with, and in all cases the indirectly elicited contractions were immediately blocked. It should be noted that at all dose levels there was an immediate acute contraction of the muscle, presumably from direct irritation of the test material; as soon as the muscle relaxed, no stimuli could be transmitted indirectly to the muscle.

To compare the action of the toxin from the barracuda from Guam to the toxin from Lutjanus bohar from the Line Islands, their respective actions on this nerve-muscle preparation were checked. Figure 1 compares the reaction of the barracuda toxin at 10 μ g. per ml. to L. bohar toxin, as a similar level of purification, at 49 μ g. per ml.

Conclusions from these experiments: From the standpoint of the neuromuscular

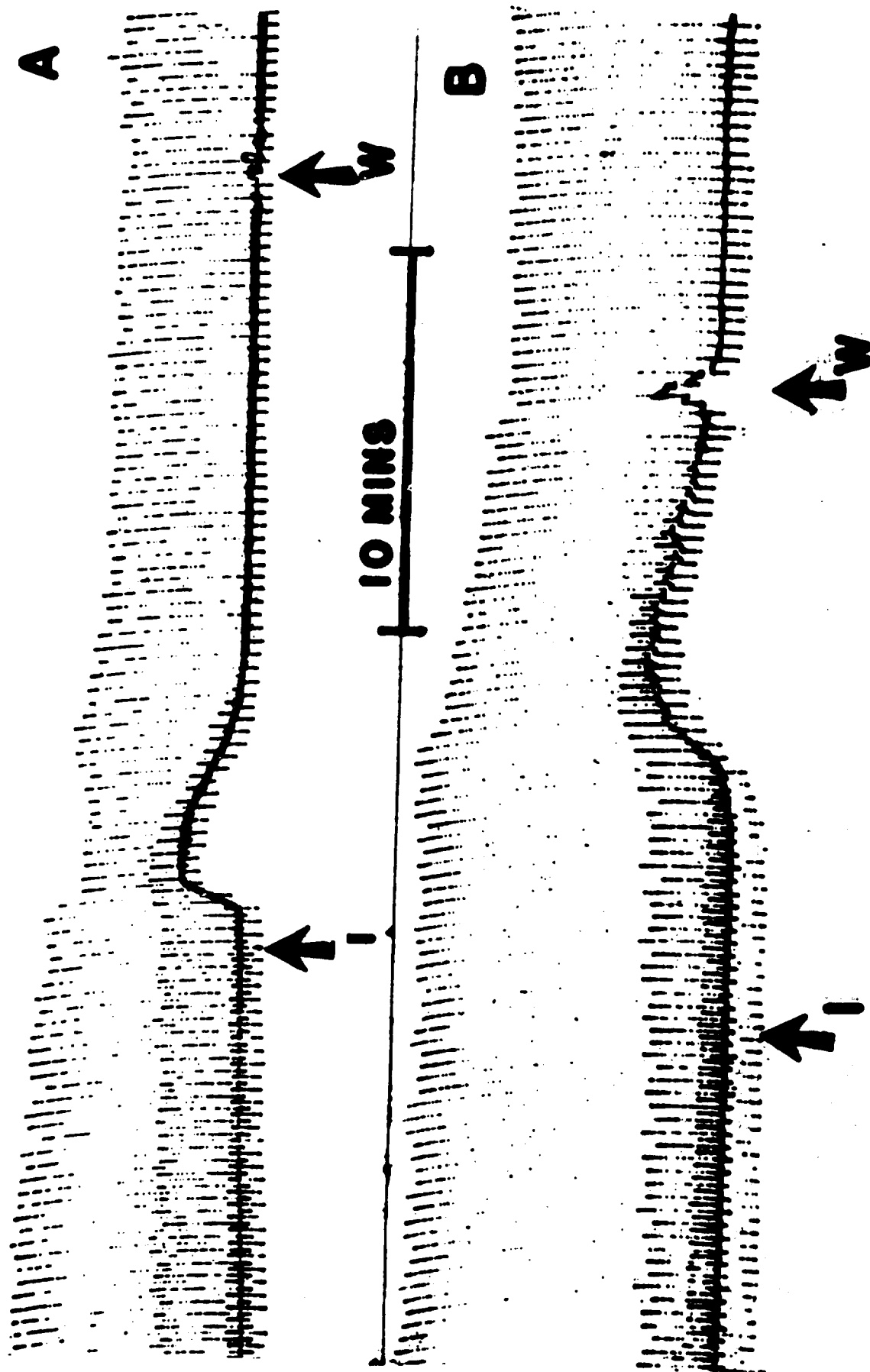


Figure 1. Comparison of effects of 10 $\mu\text{g./ml.}$ of bath of barracuda extract (A) and 40 $\mu\text{g./ml.}$ of bath of semi-purified ciguatera toxin (B) on the phrenic nerve diaphragm preparation.

I indicates injection of extract; W indicates washing of preparation.

blockage, the barracuda causing the intoxication of the patient on Guam appears to have carried a toxin similar to that found in L. bohar from the Line Islands, and the concentration of the toxin in the flesh was approximately at the level in L. bohar that has been classified as "highly toxic" (Banner et al., 1960).

Case History 2

A 31-year old Caucasian U.S. Naval Officer ate some raw ulua (pompano or jack, species unknown) that had been caught on Midway Island and kept under refrigeration until it was eaten. The fish was eaten at the evening meal on 24 October; within two hours the patient developed the initial symptoms of nausea and fatigue; he felt faint. During the first night there were chills and fever, accompanied by profuse sweating; soon there developed itching and burning of the mouth and throat, and burning of the skin "like sunburn"; in his mouth and on his hands there was a "reversal of sensation" in respect to hot and cold objects; rubbing his skin on the lower extremities gave a burning sensation; his back and legs ached and his neck was stiff, walking was difficult and there was an estimated 25% loss in strength; he had persistent nausea and diarrhoea. He was treated initially for pharyngitis on Midway; by 31 October he had returned to Hawaii where he was treated by Dr. Robert L. Altman, of the U.S. Naval Shipyard Dispensary at Pearl Harbor.

Dr. Altman, after contact with the senior author, initiated treatment with 0.25 mg. of neostigmine, administered intramuscularly every six hours (no oral preparation was available). Dr. Altman reported, "Within the first 30 minutes [after each injection, the patient would have] easing of pains in the legs; within 1½ - 2 hours, paresthesia in legs would disappear; within 5 - 6 hours pain returned; sensory reversal was 50% improved." The therapy was continued for one week. Mild symptoms returned at the end of the therapy but disappeared completely at the end of 18 - 20 days after the initial attack.

Case History 3

In April 1962 Alexander Panuelo, Acting District Director of Public Health at Ponape, Caroline Islands, had as patients 26 adults and children displaying ciguatera after having eaten two large barracuda, Sphyræna forsteri Cuvier and Valenciennes (details taken from special report of Ponape Hospital to U.S. Trust Territory headquarters).

The first fish, eaten by 17 adults and children, was eaten raw, boiled or fried. About 3.5 hours after eating the fish, the individuals displayed symptoms beginning "with numbness around the lips, then tingling sensation of the extremities followed by general weakness, carpopedal spasms, paralysis of the extremities and partial paralysis of the vocal cords, reflexes were absent. The patients could not talk but had no trouble in breathing. There were no abdominal

cramps, vomiting or diarrhoea [*italics his*]." Each adult patient Dr. Panuelo treated as follows (with correspondingly less for children):

1. Atropine, 0.01 grains, intravenously (stat.).
2. Neostigmine, 0.5 mg., intramuscularly, hourly for 8 hours.
3. Tripeleennamine (PBZ^R)¹, 30 mg., orally.
4. Dextrose in water, 1000 ml., intravenously.

In six hours there was "complete recovery of all patients."

In the other 9 persons who were admitted to the hospital 18 hours after eating the second barracuda, the symptoms were different. "... numbness of the extremities and lips with generalized weakness, abdominal cramps, diarrhoea and vomiting. No spasms or paralysis [*italics his*]." These patients were treated as the group above, and four "recovered fully within 12 hours, but after 40 hours five were still complaining of numbness and weakness of the extremities."

Based on the experience obtained in Case No. 1 above, one of us (S.W. Shaw) has written a suggested plan of treatment. This plan was circulated to medical authorities in the U.S. Trust Territory of the Pacific Islands and to Hawaii, and it was the basis for the treatment in Cases No. 2 and No. 3 above.

Discussion

The pharmacology of the toxin indicates that, while the action potential of the nerve may be lost from long immersion in a solution of the semi-purified toxin, the immediate effect is upon the nerve-muscle junction. This action could be similar to the end plate blocking action of d-tubocurarine, to the depolarizing block induced by decamethonium, or by the inhibition of the release of acetylcholine from nerve endings as caused by botulism toxin. The effective use of edrophonium-neostigmine therapy in the Guam case, of atropine-neostigmine therapy in the 21 of the 26 cases on Ponape, and of neostigmine alone in the Midway case would indicate that at least part of the symptomology of ciguatera is from the "curare-like" effects of the toxin. This is supported by Dr. Shaw's observation of a lack of fasciculation and the peripheral type left facial paresis in the Guam case which subsided with neostigmine. The role of atropine in the therapy is not understood; from the Guam case it appears that hydrocortisone is also valuable for treatment.

1. 2-[Benzyl(2-dimethylaminoethyl) amino]-pyridine, C₁₆H₂₁N₃.

SUMMARY

↙ Certain characteristics of the toxin causing ciguatera are reviewed, and it has been pointed out that there is no method of recognizing specific fish which may bear the toxin, nor of detecting the toxin in a fish except by feeding tests, nor of destroying the toxin by any normal means of food preparation. Some aspects of the pharmacology of the toxin and a possible similarity in action of the toxin to the curariform drugs are discussed. Case histories are presented in which recovery, partial or complete, might be attributed to neostigmine or neostigmine-Tensilon therapy. Chemical and pharmacological studies are reviewed which show similarities between the toxin found in a barracuda from Guam and red snappers from the Line Islands. () ←

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