THE ETIOLOGY AND EPIDEMIOLOGY PARALYTIC SHELLFISH POISONING

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Outbreaks of paralytic poisoning following the consumption of toxic shellfish have resulted in more than forty deaths in coastal areas of North America since 1927. The toxic agent exists frequently in members of the plankton species, Gonyaulax, which frequently occur in the food supply of edible shellfish. The establishment of quarantine measures based upon periodic sampling and assay of shellfish from dangerous areas, has greatly reduced the hazard to public health.

Until comparatively recent times, the utilization of shellfish foods was largely confined to maritime communities. Within the past twenty years, however, as a result of improved methods of processing, storage, and transportation their use as food on this continent by coastal and inland dwellers alike, has increased to an extent scarcely realized by many persons. The shellfish industry is now one of major economic importance to both Canada and the United States, the combined output of the two countries amounting to approximately 600 million pounds annually.

Shellfish, unfortunately, in common with many other desirable foods, are occasionally responsible for human illness, and even death. For that reason, the origin and consequences of their toxic properties has presented a problem of considerable magnitude to those agencies entrusted with the protection of public health. In consequence, many investigations into the nature and distribution of toxicity in shellfish have been conducted over the past thirty years in efforts to ensure their safety as food.

Outbreaks of food-poisoning in which shellfish have been incriminated, are of two distinct types. The first of these is characterized primarily by gastro-intestinal disorders and is considered due to contamination either with specific organisms pathogenic to man, or to massive non-specific bacterial growth arising from improper processing or storage. It may originate in varieties of food other than shellfish. The second or paralytic form of poisoning, to which the present discussion is limited, is associated with the presence of a unique toxin whose principal action is upon the central nervous system. It may be readily extracted from bacteriologically clean shellfish, and has been reported only in conjunction with species such as clams, mussels, and scallops.

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During the past fifty years, many hypotheses have been advanced as to the origin of the paralytic toxin in shellfish. Some investigators considered it to be elaborated as the result of actual disease in the mollusc. Others believed it to be a post-mortem decomposition product of the tissue, or to originate in bacterial contamination from polluted or stagnant waters.

These theories, however, were eventually abandoned following the isolation of a highly toxic substance from the dinoflagellate plankton Gonyaulax catenella, by the late Dr. Hermann Sommer and his associates of the Hooper Foundation (13). Evidence then presented demonstrated a close relationship between the toxicity of the mussel, Mytilus californianus, and the plankton concentration of the waters of their habitat. Extracts of the dinoflagellate moreover, when injected into mice, caused death with paralytic symptoms identical to those observed when toxic mussel preparations were employed. Further large-scale collections of marine plankton rich in the suspect organism were pro-
cessed by Riegel et al. (8), and yielded paralytic toxin of extremely high potency. These observations definitively established Gonyaulax catenella as the major primary source of poison in Pacific Coast shellfish.

A similar relationship between plankton concentration and the degree of toxicity in several species of Atlantic Coast bivalves has been reported by Medcof and others (5), and later confirmed by Needler (6). In both studies evidence was presented to show that a related dinoflagellate, Gonyaulax tamarensis, occurring in the planktonic food of Eastern Canadian shellfish was the major cause of their periodic toxicity. Although extraction of the toxic agent from the latter plankton has not been reported, it is generally believed to be physiologically, if not chemically, similar to that occurring in G. catenella.

Both plankton organisms exhibit a fairly well-defined seasonal pattern in growth, occurring in greatest number during the summer months. In general, therefore, the occurrence of toxicity in both Atlantic and California shellfish is also seasonal in nature, although reaching its maximum slightly later than that of the plankton count. Toxicity apparently tends to accumulate as the shellfish feed on toxic plankton, and to diminish slowly after the cause is removed. Needler (6) has shown that toxicity in the Fundy mussel, Mytilus, first appears in the early summer, more or less rapidly reaches a maximum which may persist for three or four weeks, and gradually disappears. Toxicity during the winter months is seldom observed, except in a few locations where it exists to a moderate degree throughout the year.

No such clearly defined seasonal fluctuations in toxicity have been found in the butter clam, Saxidomus giganteus, however. This species, common to the British Columbia and Alaska coasts, is equally toxic in winter as in summer, exhibiting only minor variations over long periods of time. Although little information is available concerning seasonal variations in the plankton count of western waters, this characteristic of the butter clam would suggest that G. catenella is present to some extent in the North Pacific throughout the year.

A second factor which exerts a definite effect upon the incidence of shellfish toxicity is that of coastal topography. Examination of those locations in both Atlantic and Pacific waters where toxic bivalves occur, reveals considerable physical similarity between such areas on the respective coasts. Toxicity is almost entirely confined to locations in which the shellfish beds are exposed in part to the open sea, or to large bays or inlets where active tidal currents bring ocean conditions close to shore. Shellfish from beaches protected by reefs and islands, or from enclosed inlets, on the contrary, exhibit little or no toxicity.

As might be expected, therefore, shellfish display marked variations in toxicity according to species. Shellfish whose normal habitat is within protected waters are rarely toxic; species capable of withstanding exposure to open waters may become highly toxic because of the greater availability of toxic plankton under those conditions. Individual species show a similar variation with respect to location. The butter clam, Saxidomus giganteus, on the lower British Columbia coast where it is protected from ocean conditions by Vancouver Island, is seldom toxic. However, on the western coast, and on the northern tip of that island, the species is invariably toxic to some degree.

On the Pacific coast, the shellfish species most commonly involved in outbreaks of paralytic poisoning is the large sea mussel, Mytilus californianus. Although of little economic importance, the mussel is frequently consumed by local inhabitants, and consequently has been responsible for a number of fatalities, in areas ranging from California to Alaska. Second in importance are the clams, Saxidomus nutalli, and S. giganteus, the former being native to Washington and Oregon, and the latter to British Columbia and Alaska. Both are of commercial value, and at times exhibit dangerous toxicity. The little neck clam, Paphia staminea, and the razor clam although occasionally reported as toxic on the California coast, are rarely so in more northerly waters.

Six species of shellfish on the Atlantic Coast have been reported by Medcof et al. (5) as showing varying degrees of toxicity. Of these, the most highly toxic were the horse mussel, Modiolus modiolus, and the black mussel, Mytilus edulis, followed by the bar clam and the razor clam. The commercially important species, the soft shell clam, Mya arenaria, and the scallop, Pecten grandis, although of lesser toxicity, frequently attain dangerous levels, and on occasion have caused death.

Sommer and Meyer (9) concluded that most of the poison in the large sea mussels was concentrated in the digestive glands or 'livers'. This was also noted in Atlantic shellfish, with the exception of the bar and soft shell clams. In these species, the gills were found to be an equally important center of concentration. Pugsley (7), however, demonstrated that the bulk of the toxin in the Pacific Coast butter clam, occurred in the siphon. Data later presented by Chambers and Magnusson (2) indicated that up to 70 per cent of all toxic material was located in that region. The toxicity of the siphon, moreover, exhibited marked fluctuations from month to month, but that of the body remained relatively constant. In commercially processed shellfish, however, removal of the viscera, gills, and siphons, reduces considerably the hazard to the consumer.
Paralytic shellfish toxin, whose chemical properties have been fully described by Sommer and co-authors (11) is considered to be an alkaloid, and one of the most potent known to man. It is heat stable in neutral and acid solution, but readily destroyed under alkaline conditions. The poison is freely soluble in water, acids, and the lower alcohols, but insoluble in immiscible solvents such as ether and chloroform.

Isolation of the poison in relatively pure form has been accomplished by the use of chromatographic procedures developed by Sommer et al. (11) and (12). By this method, toxic material has been prepared of such potency that as little as 0.25 microgram is sufficient to kill a mouse (3). Investigations by the author, now in progress, have shown the synthetic ion-exchange resin, Amberlite IRC-50 to be a particularly efficient adsorbant for the removal of toxin from shellfish extracts of low potency. The poison from crude extracts is rapidly and completely adsorbed by the resin, and readily eluted by small volumes of 1.0 N. HCl. Further adsorption from the acid solution on Norite and subsequent elution with alcohol, yields preparations in which the toxin concentration is increased nearly two hundred-fold in relation to that of extraneous materials.3 The ultimate purification of the toxin and its chemical structure, however, have not yet been reported.

Up to the present, no satisfactory chemical procedure for the detection and estimation of the toxic agent has been devised. Measurements of shellfish toxicity therefore, can only be determined by means of a suitable biological assay. The procedure currently employed by most investigators for the routine assay of shellfish extracts is a modification of the “field test” originally proposed by Sommer and Meyer (9). In this method, acid-aqueous extracts of shellfish are prepared according to standard procedures elsewhere described (5). 1.0 ml volumes of the extract are injected intraperitoneally into each of three albino mice weighing approximately 20 gm., and the time from injection until death is noted. The death times are referred to a standard curve from which the toxicity of the extract is determined in terms of “mouse units” per 100 gm. of shellfish tissue. The “mouse unit” is defined as that quantity of toxin which will cause the death of a 20-gm. mouse in 15 minutes, with paralytic symptoms.

Because of many variables inherent to the biological assay which are difficult to control, toxicity data from different sources can be satisfactorily evaluated only when expressed in terms of a single reference standard. With the object of developing a toxic preparation with characteristics suitable for this purpose, a study of the stability of the paralytic toxin from two species of shellfish was initiated by Stephenson et al. (14). These authors showed that a crude acid-aqueous extract, dried by lyophilization, retained its potency over long periods of time, and suggested its applicability as a biological standard.

In conjunction with this investigation, a comparison was made of both the quantal and graded response assays. When equal numbers of mice were used, the two methods appeared to measure toxicity equally well. The quantal response assays, however, possessed the added advantage that the experimental data could be more readily assessed by standard statistical procedures. It was found by these workers that female mice were considerably more susceptible to shellfish toxin than were males, and that the estimated toxicity in terms of the LD50 was dependent upon the body weight of the test animals. It was further noted that the slopes of the dosage-response lines determined for the butter clams, Saxidomus giganteus, and the Atlantic scallop, respectively, did not differ significantly. This observation suggested that the physiological action of the toxin derived from C. catenella is identical to that occurring in C. tamarensis. If this assumption can be verified, the toxicity of shellfish from different sources may then be determined in terms of a single reference standard.

Historically, one of the earliest recorded outbreaks of shellfish poisoning occurred in British Columbia waters in 1793, and is described by Captain George Vancouver in the journal of his Pacific voyages. On this occasion, four members of Vancouver’s crew having eaten mussels, became seriously ill. Of these men, one died within a few hours; the others slowly recovered. The symptoms as described in the journal were typical of the paralytic form of poisoning.

At irregular intervals during the following hundred years similar cases of poisoning were reported from a number of localities in Europe. One such outbreak in 1885, in Germany, claimed four lives, and marked the first serious attempt to isolate the toxic agent. In this study, Brieger (1) obtained a substance he called “Mytilotoxine” from mussels, which when injected
into animals produced the characteristic paralytic symptoms.

Paralytic poisoning, due to the consumption of toxic shellfish has therefore been recognized as a distinct clinical entity for more than a century. Its significance as a potential public health hazard on the North America continent however, was not fully realized until the publication in 1937 of the results of an epidemiological survey by Sommer and Meyer (9). A later report by these authors (10) recorded a total of 346 cases of shellfish poisoning, accompanied by 24 deaths, on the Pacific coast from Mexico to Alaska during the years 1927 to 1941. Since that time, 12 additional deaths have been reported in western waters.

Included in the latter outbreaks, are the first modern cases of shellfish poisoning in British Columbia, when in May, 1942, three persons died after eating clams and mussels near Bamfield on the West coast of Vancouver Island. During the same week, three fatalities also occurred in the vicinity of Port Angeles, Washington, the toxicity on both occasions presumably being due to the same widely spread body of plankton.

As recently as June, 1954, seven cases of severe illness resulting in one death were reported from False Pass, Alaska, following consumption of the mussel, Mytilus edulis. In this instance, the victim exhibited symptoms of paralytic poisoning, accompanied by abdominal pain, nausea, and vomiting, and succumbed within three hours of ingesting the shellfish. The others recovered without incident within two days.

Although information is not available as to the quantity of shellfish eaten, and their toxicity at the time, samples of mussels collected three weeks later were found to contain on the average, 86,000 mouse units per 100 gms. of tissue. Microscopic examination of sea water samples taken then, indicated that G. catenella was present, but not in large numbers, suggesting that the plankton had disappeared in the time that had elapsed between the poisonings and collection of specimens.

On the Atlantic coast of Canada, a comparable situation was found to exist, following the occurrence of two deaths from the use of toxic mussels at Digby, Nova Scotia. This was confirmed by Gibbard and co-authors (4), who demonstrated the presence of paralytic toxin in several species of shellfish from the Bay of Fundy.

As a result of the increased war-time demand for shellfish products of all kinds, and because of the apparent risk, further studies of Atlantic coast conditions were instituted in 1943 by the Department of National Health and Welfare in co-operation with the Department of Fisheries, and the Fisheries Research Board of Canada. Epidemiological data obtained in the course of this survey have been reported by Medcof and others (5). These authors described in detail, the symptoms, their sequence, and the probable quantity of toxin ingested by 21 victims of shellfish poisoning in New Brunswick in August, 1945. The shellfish concerned in these cases was the soft shell clam, whose toxicity in the raw state amounted to 18,000 mouse units per 100 gm. of meat. Depending upon the quantity of food consumed, the dosage of ingested toxin was estimated to vary from 1000 to 36,000 mouse units in the individual cases. No fatalities occurred, and the symptoms were arbitrarily classed as mild, severe, and extreme.

In this study, wide variations in human susceptibility to the toxin were noted. Some victims who consumed at little as 4,000 mouse units were seriously ill, while others ingesting 11,000 presented only mild symptoms. Still others received dosages estimated at 17,000 mouse units without harmful effects. Data also presented by these authors suggested that certain persons possess a natural tolerance to paralytic toxin; others, resident in coastal areas whose diet normally includes shellfish, may acquire a tolerance to quantities of poison that would produce severe symptoms in susceptible individuals.

From the information available, many investigators have concluded that the minimum lethal dose of shellfish toxin for man, is probably between 30,000 and 40,000 mouse units. The minimum amounts of poison producing mild, severe, and extreme symptoms have been estimated at approximately 2,000, 10,000 and 20,000 mouse units respectively. Somewhat lower values than these, however, were evident from an outbreak of poisoning at Metis Beach, Quebec, in July 1954. On this occasion, the consumption of toxic clams resulted in illness and two deaths in the seven members of one family. Death in one instance was caused by less than 12,000 mouse units, and severe illness in four others by less than 5,000 mouse units.

The symptoms of paralytic poisoning in man, as indicated earlier, are of nervous origin and may appear within less than an hour of ingesting the shellfish. A prickly sensation of the lips, tongue, and face, followed by numbness of the extremities are early signs of intoxication. In severe cases, these symptoms are succeeded by dizziness, convulsions, lack of muscular co-ordination, and varying degrees of paralysis. Lethal doses of the toxin result in death from respiratory failure. Although nausea and abdominal pain are common, other gastro-intestinal symptoms are infrequent.

No specific antidote to the toxin is known and treatment usually consists of the use of emetics and the control of shock. In the event of respiratory difficulty, artificial respiration or oxygen should be em-
played. Since the toxin is largely excreted through the kidneys, diuretics may be of value.

In the course of investigations into shellfish toxicity conducted over the past twenty-five years, it became apparent to public health authorities in both Canada and the United States that some degree of control over shellfish producing areas was necessary. Regulatory measures accordingly, were introduced by many states and provinces in order to prevent the sale and use of dangerously toxic shellfish. Since 1929, California has imposed a quarantine on mussels from May to October annually, similar action later being taken by Oregon and Washington with respect to clams as well.

On both the Atlantic and Pacific coasts of Canada, however, quarantine is based upon a continuing sampling program which has been in effect since 1942, and is applied only when toxicity levels exceed a specific amount. Under this plan as conducted in the British Columbia region, sampling areas have been selected that were considered representative of the variable conditions along the coast, and with due regard to commercial use and proximity to centres of population. Since toxicity in this region exhibits no decrease during the winter months, sampling is continued throughout the year.

On the Atlantic coast, and particularly in the Bay of Fundy, however, there is a consistent order in the time of appearance of toxicity in different locations. Mussels in areas exposed to the open bay, regularly show poison about ten days prior to its presence in tributary inlets. For this reason, regular sampling from a few selected "key stations" provides sufficient warning for the imposition of quarantine measures.

Information gained from early studies indicated that commercial processing and domestic cooking usually destroyed up to 90 per cent of the toxin initially present. In spite of this reduction, however, persons who consume large quantities of shellfish may still ingest sufficient poison when original toxicity is high, to induce severe illness. In order to provide a wide margin of safety in such cases and to allow for sampling variation and assay errors, quarantine levels have been established at the relatively low value of 400 mouse units per 100 gms. of tissue. When toxicities exceed this amount, removal of shellfish from the beaches concerned is prohibited.

Surveys on the Atlantic coast have shown that shellfish toxicity in dangerous years may attain values of 36,000 mouse units or more. In the British Columbia butter clam, toxicities greater than 5,000 mouse units have been the exception. Values of 1500 units commonly occur in the vicinity of Prince Rupert, and occasionally on the West coast of Vancouver Island. These values, although not as extreme as those of the Fundy area, are still capable of causing illness or death in susceptible persons. The efficiency of the quarantine system is thus evident from the fact that no cases of poisoning attributable to commercially produced shellfish have occurred since its inception.

Paralytic shellfish poisoning is therefore a problem of mutual concern to health and fisheries agencies of both the United States and Canada. Parallel regulatory measures in the two countries, and the free exchange of information, have greatly reduced this hazard to public health.

References