Drugs from the Sea

Marine organisms with novel chemical constituents are excellent sources of new drugs.

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Ancient maritime peoples, notably the Chinese and Japanese, ate a variety of iodine-rich seaweeds that undoubtedly accounted for their low incidence of goiter. They also used certain seaweeds as medicinals. An early Chinese pharmacopoeia recommended seaweeds for such diverse maladies as dropsy, menstrual difficulties, abscesses, and cancer. A mixture of seven seaweeds served as a vermifuge (*1*), and a derivative of agar was used for gastrointestinal disorders (*2*). Classical writers in the West did not share the Oriental enthusiasm for seaweeds. Virgil and Horace were both convinced that there was nothing more vile than algae: "*nihil vilior alga*"! This, in spite of the fact that their Roman ladies used rouge made from a red seaweed and bedecked themselves in beautiful gowns dyed purple with a seaweed extract (*1*). Almost 75 years later, another Roman attributed some rather bizarre medicinal effects to marine animals. Pliny the Elder suggested that the cinders from the burnt spine of a stingray mixed with vinegar would alleviate the pain of toothache. And a pregnant woman would be assured of an easy childbirth if she wore a stingray spine around her navel, but only if the spine was removed from a living ray; the ray would have to be returned alive to the sea. Although Pliny did not recommend the poison from the sea hare as an abortifacient, he considered this naked mollusk's toxin to be so potent that if a pregnant woman even looked at it she would feel immediate pain, become nauseous, and abort (*3*).

The search for drugs from the sea is a relatively recent undertaking. Early studies on the chemistry of marine organisms were the domain of organic chemists, most of whom were concerned with the isolation, chemical characterization, and phylogenetic variants of specific substances, for example, types of sterols present in diverse marine animals. A symposium held in 1960 on the biochemistry and pharmacology of compounds derived from marine organisms brought researchers together for the first time and gave cohesion and direction to this field (*4*). Workers in many disciplines became involved, including structural chemists, marine biologists, pharmacologists, microbiologists, and ethologists. Four subsequent symposia on food and drugs from the sea (*5*), and the recently established Gordon Research Conference on marine natural products, attest to the progress made by this multidisciplinary approach (*5*). Two recent books, *The Chemistry of Marine Natural Products* by Scheuer, and *Compounds from Marine Organisms* by Baker and Murphy, and review articles by Premuzic and by Faulkner and Andersen describe some of the active compounds from marine organisms that have been structurally defined (*6*).

Some marine organisms are venomous or poisonous. Because toxicity is indicative of potent physiological activity, it is likely that some of the toxins from marine organisms will yield new compounds having marked pharmacological activities. The biology, chemistry, pharmacology, clinical aspects, and treatment of envenomations by toxic marine animals are reviewed by Halstead and by Russell (*7*). Many other compounds from marine organisms have inhibitory effects on a variety of microorganisms that cause disease in man. Such natural products may enter directly the realm of *Materia Medica* or they may serve as models for the synthesis of new and effective drugs.

Seaweeds and Phytoplankton

Marine algae vary in size from minute unicellular forms of a few microns in diameter to the large seaweeds that are many meters in length. Algae are not only the primary and major producers of organic matter in the sea, but they also exert profound effects upon the density and distribution of the other inhabitants of the marine environment. Some of the effects, for example, red tide outbreaks, result in massive fish kills. An understanding of the wide range of behavioral relationships that exist among organisms would not only increase our appreciation of the organisms themselves but would also provide us with clues to substances of biomedical interest.

In 1888, Stahl noted that terrestrial plants evolved toxic "secondary" substances as protective devices against excessive predation. "Thus, the animal world which surrounds the plants deeply influenced not only their morphology, but also their chemistry" (*8*). The noxious plants, in turn, influenced the development of animals (for example, insects), and herbivores evolved that actually require "repellants" as feeding attractants. Thus, some plant-animal relationships became more intricate and, in certain cases, highly specific. For example, the sea hare *Aplysia californica*, a slow-moving, sluglike animal feeds upon the red alga *Laurencia pacifica*, and utilizes some of the toxic metabolites of this seaweed (*9*). The seaweed not only provides the adult tectibranch with compounds that protect it from predators, it also appears to be essential for metamorphosis of the sea hare larvae: veliger larvae of *Aplysia* will not metamorphose into benthic juvenile sea hares unless they settle upon *L. pacifica* (*10*). Chemical cues of this type, that are active at very low concentrations, play important roles in many of the behavioral responses elicited by and among organisms in the marine environment (*11*).

Some Antarctic penguins have "sterile" gastrointestinal tracts. These pygoscelid penguins eat the euphausid krill (*Euphausia superba*) that grazes upon the brownish-green colonial alga, *Phaeocystis pouchetii*. The alga contains acrylic acid, an antibacterial agent that is responsible for the paucity of microbes in the gut of the penguins (*12*). This alga also has an adverse effect upon herring; whenever North Sea fishermen encounter dense patches of this mucilaginous alga clinging to their nets, they know that few if any herring will be caught (*13*). The succession of organisms in the marine environment is due, at least in part, to growth-inhibiting and growth-promoting substances secreted, excreted, or released by decomposition by one or more members of the community (*14*). A number of seaweeds contain antimicrobial

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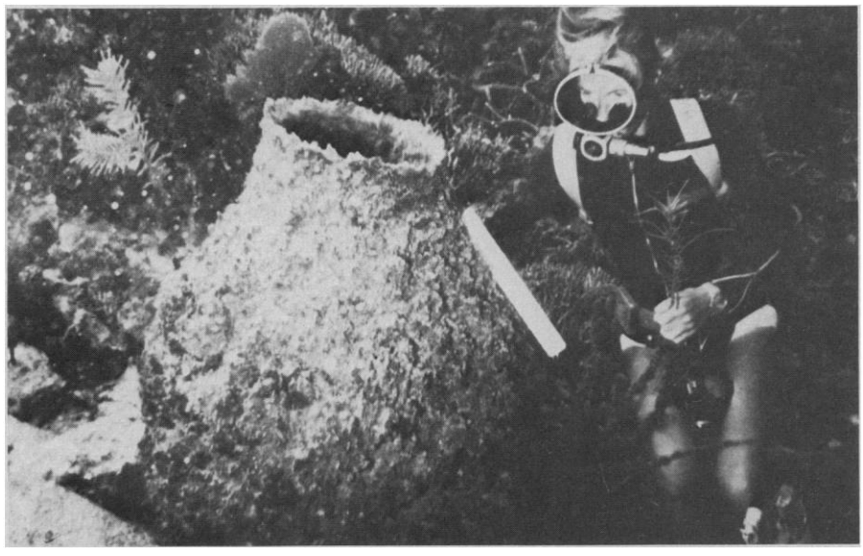

Fig. 1. The sponge *Verongia gigantea* possesses antibacterial substances. [Courtesy of the Osborn Laboratories of Marine Sciences]

substances that vary according to the season: specimens collected during the winter are devoid of antibacterial effects (*15*). Antibacterial substances are found also in marine phytoplankton (*16*) and in intracellular algae of marine invertebrates (*17*). Some marine algae are active against fungi (*18*). In addition, the antibiotic substances present in *Sargassum natans* (*19*) are effective in reducing mortality in chicks infected with *Salmonella gallinarum* (*20*).

Alginates, Agar, Carrageenan

Alginates from brown (Phaeophyceae) seaweeds, and agar and carrageenan from red (Rhodophyceae) seaweeds, are used extensively in the food, cosmetic, pharmaceutical, and other industries. An extract from a red seaweed soothed throat irritations of soldiers who had been gassed during World War I (*1*). Carrageenan denatured with whiskey was highly recommended for coughs in a number of Hibernian bars in New York, and had predictably good results. Carrageenan prolongs the activity of commonly used analgesic and antitussive agents such as codeine and ethylmorphine, and is incorporated in tablets containing these drugs to promote rapid disintegration.

Calcium alginate woven into surgical dressings forms a gel and arrests bleeding. Because of its hemostatic quality, alginate wool is used widely in dentistry. Ebimar, a sulfated polysaccharide extracted from the Irish moss *Chondrus crispus*, is an effective antacid (*21*), and kainic acid obtained from *Digenia simplex*, a red seaweed, is widely used as an ascaricide in Japan (*21*, *22*). Agar is unrivaled for plate culture of bacteria. Sulfated polysaccharides in agar are inhibitory against a number of animal viruses in vitro, including picornaviruses, aborviruses, myxoviruses, and herpesviruses (*23*). Carrageenan and polysaccharide-containing substances extracted from *Gelidium cartilagineum* markedly inhibit the growth of influenza B and mumps viruses in embryonated chick eggs but have no effect on influenza A virus (*24*).

Extracts of seaweeds are also beneficial as a coadjuvant in cancer therapy. Recovery from bone metastases was rated as good in 68 percent and moderately good in 19 percent of 162 patients who were administered an algal phycocolloid after surgery or x-ray therapy. The treated patients were free of nausea, had improved appetites, a decrease of asthenia, and less painful symptoms than those normally associated with this form of cancer (*25*).

Carrageenan, when administered to dogs and guinea pigs, protected the animals against histamine-induced gastroduodenal ulceration by enhancing the mucoid function of the lining of the mucosa and by reducing the volume and acidity of gastric secretion by as much as 50 percent (*26*). Intravenous injections of carrageenan and of laminarin sulfate from *Laminaria digitata* significantly lowered serum lipids and prevented the development of atherosclerosis (*27*). Laminarin sulfate acted like heparin in clearing alimentary lipemia and in prolonging coagulation time in dogs, rats, and rabbits (*28*). Highly sulfated laminarins are both anticoagulant and antilipemic, but laminarins with few sulfate groups are antilipemic only (*21*, *29*). Sodium alginate, funoran, and carrageenan are highly hypocholesterolemic. These acidic polysaccharides are soluble in water and form an indigestible lyophilic colloid that prevents the absorption of cholesterol from the gut. But agar, a neutral polysaccharide which rarely forms a lyophilic colloid, is ineffective as a hypocholesterolemic agent (*30*). Certain seaweeds that are commonly eaten in Japan also reduce plasma cholesterol levels in rats (*31*).

Alginates and Radioactive Intoxication

Alginates prevent the intestinal absorption of radioactive strontium without significantly affecting the absorption of radioactive calcium (*32*). Radioactive strontium forms an insoluble strontium alginate gel in the gastrointestinal tract which is excreted in the feces without damaging the body. Partial acid hydrolysis of alginic acid yields degradation products that have a higher percentage of guluronic acid than mannuronic acid and are more effective than the parent alginate in preventing the absorption of radioactive strontium (*33*). Even higher amounts of guluronic acid are obtained by using enzymes from the hepatopancreas of the abalone, *Haliotis discus* (*34*). Alginates rich in guluronic acid residues are known to have a greater affinity for divalent metals than mannuronic-rich alginates, and they also have a higher selective binding capacity for strontium than calcium (*33*, *35*). Alginates can be used both for preventing and for the treatment of radioactive strontium poisoning; radioactive strontium already deposited in bone is resecreted into the intestine where it is bound by alginate and excreted in the feces (*36*).

Carrageenan from the seaweed *Hypnea japonica*, after reduction with sodium borohydride, increases calcium uptake in the bone and decreases serum calcium (*37*). Further, since certain common seaweeds, such as *Enteromorpha intestinalis* and *Cladophora rupestris*, assimilate radioactive substances from the sea, it might be possible to use them for monitoring radioactive contamination in seawater (*38*).

Rats given an overdose of barium, cadmium, or zinc survive the poisoning if they are given simultaneously an oral dose of acid algal polysaccharides (*39*). This suggests that algal polysaccharides might be used in preventing intoxication from certain metal pollutants.

Marine Invertebrates

The diversity of form and physiological competence of marine invertebrates contributes to their usefulness in medical research (*40*). The invertebrate phyla most intensively studied for the presence of biologically active substances have been those most readily available. For example, sponges, cnidarians, polychaete worms, mollusks, and echinoderms are easily acquired in quantities sufficient for chemical extraction and biological testing. However, new and improved methods of extraction, coupled with the development of more sensitive assays, are increasing the number of studies being conducted on less readily available invertebrates whose life modes suggest interesting chemical constituents (*41*).

Fig. 2. A sponge, *Agelas* sp., which possesses antibacterial substances. [Courtesy of the Osborn Laboratories of Marine Sciences]

Sponges

There are some 5000 species of sponges, and most of them are marine. Broad spectrum antibiotics have been extracted from a variety of marine sponges (*42*) (Figs. 1 and 2). Extracts of some sponges are cytotoxic to KB cells (human oral carcinoma) and to HeLa cells (human cervical carcinoma) in vitro (*43*). Halitoxin from *Haliclona viridis* reduced the mortality of mice inoculated with Erhlich ascites tumor cells, and an extract from *Chondrilla nucula* extended the survival time of mice with lymphocytic leukemia (*44*, *45*).

The discovery that the Caribbean sponge *Tethya crypta* (Fig. 3) contains copious amounts of arabinosyl nucleosides (*46*) focused attention on these compounds and led to the synthesis of 1-β-D-arabinofuranosylcytosine (ara-C) (*47*). Evans *et al.* (*48*) found this substance to be a potent inhibitor of such tumors as sarcoma-180, Erhlich carcinoma, and L1210 leukemia in mice (*48*). Moreover, ara-C was also found to be highly active against acute myelogenous leukemia, and in one study induced complete remission in nearly 30 percent of the patients to whom it was given. A higher rate of remission (50 percent) was obtained when ara-C was used in combination with other drugs (*49*).

Corals, Jellyfish, Sea Anemones

The corals, jellyfish, and sea anemones belong to the phylum Cnidaria, and there are approximately 11,000 species of these predominantly marine organisms. Antimicrobial substances occur in various gorgonian corals (class Anthozoa) such as *Antillogorgia turgida*, *Rhipidogorgia flabellum*, and *Plexaura homomalla* (*50*). Water-soluble materials from ethanolic extracts of eight Hawaiian species of the anthozoan subclass Zoantharia inhibit the growth of Erhlich ascites carcinoma in mice. The Erhlich ascites–active material appears to be the toxin itself, since increased antitumor activity parallels increased toxicity (*51*). Aequorin, the bioluminescent protein present in the jellyfish *Aequorea aequorea*, glows in the presence of calcium or strontium, and is sensitive enough to detect minute fluctuations in calcium concentrations in biological fluids (*52*). Because calcium changes are often reflective of cellular dysfunctions, aequorin may prove useful in diagnosing cardiac irregularities, metastatic carcinoma, and other disease processes.

Prostaglandins were first isolated from human semen and from sheep sperm and vesicular glands (*53*). They have since been found in low concentrations in nearly all mammalian organs (*54*). Only recently, however, have prostaglandins been isolated from a nonmammalian source in amounts that could be utilized as potential precursors of the natural hormones. Two prostaglandins that were found in the gorgonian *Plexaura homomalla* (*55*) were of the inactive 15*R* configuration, but samples of prostaglandins from other specimens of *P. homomalla* from a different locale possessed the active 15*S* configuration (*56*). These fatty acid–derived hormones exhibit potent physiological activities in mammals, in that they can stimulate smooth muscle, depress blood pressure, and exert tranquilizing effects on the central nervous system. The last effect is similar to that produced by reserpine and chlorpromazine (*57*).

An extract of the sea anemone *Rhodactis howesii* has an anticoagulant factor that appears to be distinct from the lethal neurotoxin and hemolysin that also occur in this anemone (*58*). Sigel *et al.* found an extract of *Gorgonia ventalina* that extended the survival time of mice with lymphocytic leukemia by 36 to 40 percent (*45*).

Segmented Worms

More than half of the 9000 species of annelids are polychaetes or bristle worms, and most of these are marine. Thelepin, extracted from the tube-dwelling polychaete *Thelepus setosus* exhibits antifungal activity at a level comparable to griseofulvin with which it has a structural resemblance (*59*). Tabrah *et al.* (*60*) found that extracts of the tentacles of two tropical marine polychaetes (*Lanice conchilega* from Hawaii and *Reteterebella queenslandia* from Australia) completely inhibited the growth of Erhlich ascites tumors in 60 to 100 percent of treated mice. Because these annelids regenerate new tentacles in several weeks,

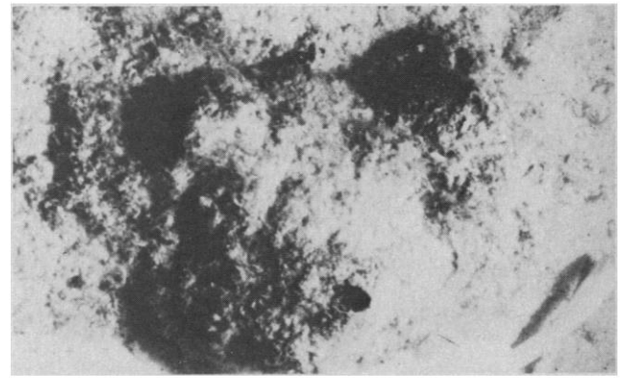

Fig. 3. *Tethya* (=*Cryptotethya*) *crypta*, a sponge that contains the arabinosyl nucleosides spongothymidine and spongouridine. [Courtesy of the Osborn Laboratories of Marine Sciences]

the same worms can be used repeatedly as sources of active material (*60*).

Japanese fishermen have known for a long time that certain carnivorous insects die when they alight upon a marine polychaete worm (*Lumbrineris brevicirra* = *Lumbriconereis heteropoda*), commonly used as bait (Fig. 4). Nitta (*61*) first isolated the neurotoxin that killed the insects and named it nereistoxin. The toxin, which is localized in the integument of *L. brevicirra*, is not present in other species of annelids that are used as bait (*62*). Nereistoxin causes a marked ganglionic blocking action in the central nervous system of insects (*63*). Its mode of action, therefore, differs from that of the chlorinated hydrocarbons and organophosphates which are used in many commercial insecticides and exert their effects by inhibiting cholinesterase. An insecticide that was developed from nereistoxin, cartap hydrochloride [1,3-bis-(carbamoythio)-2-(*N*,*N*-dimethylamino)-propane hydrochloride] has been marketed under the trade name Padan since 1967 by Takeda Chemical Industries, Japan. Padan is effective against the Colorado beetle (*Leptinotarsa decemlineata*); Mexican bean beetle (*Epilachna varivestis*); cotton-boll weevil (*Anthonomus grandis*); rice stem borer (*Chilo suppressalis*), one of the most noxious pests in Japan; cabbage butterfly (*Pieris rapae*); and diamondback moth (*Plutella maculipennis*). This insecticide is also effective against strains of insects that are resistant to organophosphates and organochlorides. Padan is essentially nontoxic to warm-blooded animals and decomposes fairly rapidly in biological tissues and in the natural environment. Except for being phytotoxic to a variety of Red Delicious apple and mature cotton leaves, Padan appears to have no deleterious effects on other crops (*64*).

Snails, Clams, Octopus

There are more than 100,000 species of mollusks. Antiviral and antibacterial substances have been extracted from the abalone, clam, oyster, queen conch, sea snail, and squid (*65*). Mercenene, an extract of the whole body of the clam, *Mercenaria mercenaria*, was found to inhibit the growth of both HeLa and KB cells in culture and Krebs-2 ascites and sarcoma 180 tumors in mice (*66*). The antitumor factor was temperature dependent: extracts of clams collected during the summer months were more active than those collected during the winter (*67*). Extracts of the whole clam and

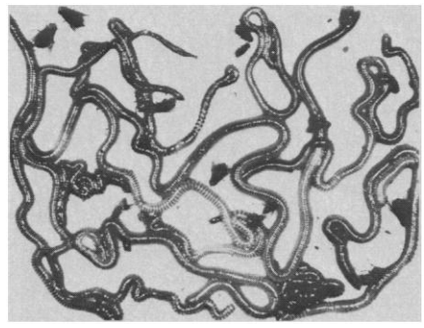

Fig. 4. Nereistoxin from this marine annelid (*Lumbrineris brevicirra*) led to the development of a highly effective insecticide. [Courtesy of Yoshiro Hashimoto and Tomotoshi Okaichi]

partially purified extracts of the clam's liver were found to have a therapeutic effect on mice with L1210-derived leukemia, a prophylactic effect against tumors induced by adenovirus type 12 in hamsters, and an inhibitory effect on murine leukemia induced by Maloney and Friend viruses. Mercenene also inhibited both Rous sarcoma virus (in vivo and in vitro) and influenza A virus in chick embryos, and caused tumor regression when injected directly into small tumors induced by adenovirus type 12 or SV-40 virus (*68*). This clam extract reduced the growth of tumors on mouse skin that had been caused by the carcinogen methylcholanthrene, reduced the regeneration rate of amputated newt limbs, and delayed the healing process of wounds in the rabbit ear (*69*). Extracts of the conch, *Strombus gigas*, were found to be active against P388-derived lymphocytic leukemia in mice (*45*).

Murexine (urocanylcholine) is present in the hypobranchial body or purple gland of *Murex trunculus* and related snails (*70*). Murexine manifests intense nicotinic and curariform actions and is used experimentally as a muscle relaxant (*21*). Eledoisin, though not present in all species of Octopoda, is a hendecapeptide found in the posterior salivary glands of *Eledone* species (*21*, *71*). When tested in dogs, this substance was 50 times more potent than acetylcholine, histamine, or bradykinin in its ability to provoke hypotension (*72*). Eledoisin stimulates extravascular smooth muscle and is a potent vasodilator and hypotensive agent in most animals, including man (*73*). The action of eledoisin appears to be chiefly peripheral, affecting vascular smooth muscle or postganglionic pathways to blood vessels, or both (*74*).

Octopamine is found in the salivary glands of *Octopus vulgaris*, *O. macropus*, and *Eledone moschata* (*75*). The D(−) form is three times more potent than the L(+) form in producing cardiovascular adrenergic responses in anesthetized dogs and cats (*21*). Approximately 1 percent of the salivary glands of the European whelk, *Neptunea antiqua*, consists of tetramine (*76*). Tetramine exhibits curare-like effects and stimulates the parasympathetic system in mammals. This substance was first reported in the sea anemone, *Actinia equina* (*77*) and later in many other Cnidaria.

Acrylcholine has been isolated from the hypobranchial gland of the gastropod, *Buccinum undatum* (*78*). It causes contraction of smooth musculature and hypotension in mammals and exerts a weak neuromuscular blocking action. Aqueous extracts of the hypobranchial gland of the gastropod, *Thais lapillus*, produce vasoconstriction and hypotension in rabbits (*79*). Senecioylcholine, present in extracts of the hypobranchial glands of *Thais floridana*, resembles urocanylcholine (murexine) but is not as potent a neuromuscular blocking agent (*78*). Extracts of two mollusks, *Macrocallista nimbosa* (from Florida), and *Turbo stenogyrus* (from Taiwan) are effective against experimentally induced P388 lymphocytic leukemia in mice (*80*).

Sea Cucumbers and Sea Stars

The approximately 6000 species of echinoderms are exclusively marine. The five classes, Crinoidea (sea lilies, feather stars), Holothuroidea (sea cucumbers), Echinoidea (sea urchins and sand dollars), Asteroidea (sea stars), and Ophiuroidea (brittle stars) are found at all latitudes and all depths. Holothurin, a steroid saponin isolated from the Bahamian sea cucumber, *Actinopyga agassizi* (Fig. 5), suppresses the growth of Krebs-2 ascites tumors and sarcoma-180 in mice (*81*). It affects the amoeboid movement and increases the phagocytic activity of leukocytes (*82*). Holothurin A irreversibly blocks cholinergic neuromuscular transmission, evokes direct contractural response from striated muscle, destroys ganglionic excitability (*83*), and modifies both excitation and conduction phenomena of myocardial cells (*84*). Holothurin-like substances from other sea cucumbers and sea stars elicit a variety of effects on a number of biological systems (*85*).

Crude extracts of the sea stars *Asterias forbesi*, *Acanthaster planci*, and *Asterina pectinifera* are effective against influenza B virus in embryonated chicks (*86*). An aqueous extract from the sea cucumber *Stichopus japonicus* is highly effective against Erhlich ascites tumors

in mice (*87*), and an antifungal steroid glycoside, holotoxin, isolated from this same sea cucumber, exhibits high activity in vitro against a variety of fungi (*88*).

A protein isolated from the coelomocytes of the sea star *Asterias forbesi* causes a delayed inflammatory response in a number of mammalian species, including humans, and inhibits macrophage migration (*89*). These and other investigations of agglutinins from marine invertebrates may prove to be useful in studies on the immunotherapy of cancer (*90*).

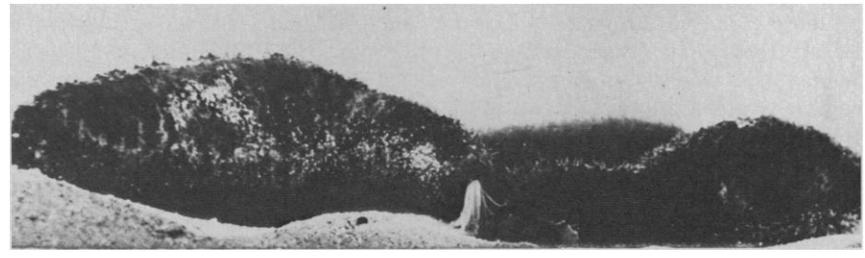

Fig. 5. Bahamian sea cucumber, *Actinopyga agassizi*, contains the steroid saponin holothurin in its Cuvierian tubules (thread-like extensions). [Courtesy of the Osborn Laboratories of Marine Sciences]

Sea Squirts

Most of the more than 2000 species of tunicates belong to the Ascidiacea, a class of the subphylum Urochordata. All ascidians are marine, living either free in sand and mud or attached to solid surfaces.

Extracts of the sea squirt *Ecteinascidia turbinata* are cytotoxic to KB cells, prolong the survival of mice implanted with leukemic cells, and diminish humoral and cellular immune responses (*45, 91*). Extracts of the ascidians, *Molgula occidentalis* and *Clavelina picta*, extend the life of mice with lymphatic leukemia (*92*) and geranylhydroquinone extracted from *Aplidium* sp., an intertidal tunicate, when administered prior to the induction of some forms of leukemia, Rous sarcoma, and mammary carcinoma in test animals prevents the growth of these cancers (*93*).

Horseshoe Crabs, Moss-Animals, and Proboscis Worms

The horseshoe crab *Limulus polyphemus* is abundant but restricted to the East Coast of the United States. Lysed blood cells (amebocytes) of the horseshoe crab form a gel in the presence of bacterial endotoxin (*94*). The lysate, therefore, is used to measure the amount of endotoxin present in animal and human blood (*95*). This in vitro test for endotoxin from Gram-negative microorganisms is more sensitive and gives results more rapidly than any other test. An extract of the horseshoe crab affords at least partial amelioration of leukemia in mice; and an extract of the bryozoan *Bugula neritina* extended the lives of mice with lymphatic leukemia by 68 to 100 percent (*45*). The adult female echiuroid, *Bonellia viridis*, releases its ciliated larvae into the sea. Larvae that settle upon the adult female develop rapidly into males that are stunted in growth, while the free larvae grow slowly and mature as females. Nigrelli *et al.* (*96*) found that extracts of the adult female inhibited KB human oral carcinoma cells in tissue culture (*96*).

Marine Vertebrates: Fishes

Cod liver oil from fresh livers of *Gadus morrhua* and other Gadidae is effective in treating hypovitaminosis A and D in humans, and is incorporated into ointments for the treatment of wounds, burns, and abscesses of animals (*21*). Halibut liver oil is also used in vitamin A and D therapy (*21*). Isinglass or fish glue obtained from the inner membrane of the swim bladder of *Acipenser huso* and other species of sturgeon and hake is sometimes used as nutrient and food instead of gelatin, and as a protective colloid in the manufacture of various chemicals (*21*). Protamines, a group of strongly basic proteins that on hydrolysis yield basic amino acids, and that occur combined with nucleic acid in the sperm of fishes (for example, salmine from salmon sperm and clupeine from herring sperm), are heparin antagonists in hemorrhagic conditions. The action of insulin in the treatment of diabetes can be prolonged if the insulin is put in a buffered medium modified by the addition of zinc chloride and protamine (*21*). Protamine isolated from the sturgeons *Acipenser guldenstadti* and *A. stellatus* inhibits solid sarcoma-37 in mice (*97*). Squalene, found in large quantities in shark liver oil, is used as a bactericide and as an intermediate in the manufacture of pharmaceuticals (*21*). Squalane, a derivative of squalene, is used as a skin lubricant, an ingredient for suppositories, and a carrier of lipid-soluble drugs (*21*).

Eptatretin from the aneural branchial hearts of the Pacific hagfish, *Eptatretus stoutii*, is a potent cardiac stimulant and hypertensive agent. This extract has a direct stimulatory action upon the mammalian myocardium similar to that produced by epinephrine and digitalis glycosides. Eptatretin also reverts spontaneous arrhythmias of the isolated frog heart to a regular beat (*98*).

A major immunoglobulin of sharks has IgM molecules that have specific antigen-binding activity (conventional antibody) and IgM molecules that possess binding sites capable of binding antigens of diverse specificities (primitive binding). Antigen binds to IgM, forming immune complexes that inhibit the response of lymphocytes to mitogen stimulation (*99*). Nurse shark serum prevents the growth of Rous sarcoma cells transplanted into the chicken (*100*); and the plasma of the stingray, *Dasyatis sabina*, is cytotoxic against leukemia L1210 cells

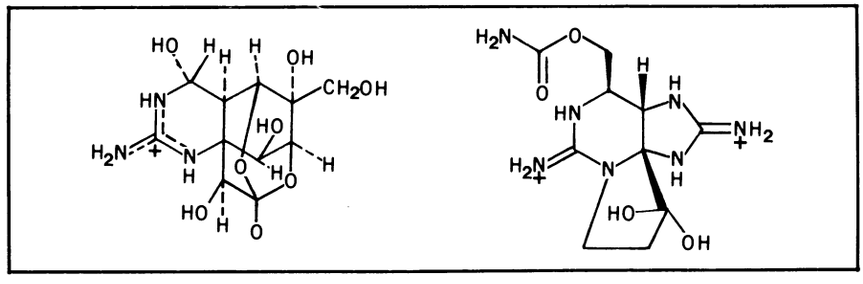

Fig. 6 (left). Structure of tetrodotoxin (*109*). Tetrodotoxin is an aminoperhydroquinazoline compound with a molecular formula of $C_{11}H_{17}N_3O_8$. It possesses one carbocyclic ring, a guanidine moiety, six hydroxy groups, and a unique hemilactal link between two separate rings. Fig. 7 (right). Structure of saxitoxin (*110*). Saxitoxin contains three rings and is a 3,4,6-trialkyl tetrahydropurine with a molecular formula of $C_{10}H_{17}N_7O_4$. It possesses no carbocyclic ring, but contains two guanidine moieties.

in vitro, inhibiting the growth of the cells by more than 96 percent in 24 hours. Plasma from *Dasyatis sayi* and from the nurse shark, *Ginglymostoma cirratum*, however, exhibit a less cytotoxic effect on leukemia L1210 cells, and that of the lemon shark, *Negaprion brevirostris*, inhibits growth by only 36 percent (*101*).

Tetrodotoxin, one of the most toxic of the low molecular weight poisons, is found in certain puffers, ocean sunfishes, and porcupine fishes. The highest concentration of the toxin occurs in the liver and ovaries, especially just prior to spawning. Tetrodotoxin is present also in the California newt, *Taricha torosa*, and other members of the genus *Taricha* (*102*), in a goby, *Gobius criniger*, from Taiwan and Amani-Ō-shima Island (*103*), and in Central American frogs of the genus *Atelopus* (*104*). The distribution of this toxin in both marine and nonmarine species is fascinating from an evolutionary viewpoint because it appears that tetrodotoxin is not exogenous in origin.

Tetrodotoxin is some 160,000 times more potent than cocaine in blocking axonal conduction. It is also unique in preventing the usual increase in permeability to sodium ions without affecting the outward potassium flow. It is useful, therefore, in the study of excitation phenomena (*105*). Tetrodotoxin is being used clinically as a muscle relaxant and pain killer in cases of neurogenic leprosy and terminal cancer and as a local anesthetic in Japan (*106*).

The only other substance that is known to act so selectively is saxitoxin (responsible for paralytic shellfish poisoning caused by certain toxin-producing dinoflagellates). Although these two substances are chemically distinct (Figs. 6 and 7), they exhibit the same clinical symptoms and have exactly the same effect on excitable membranes (*105*).

Summary and Conclusion

Many marine flora and fauna contain substances that have antiviral, antimicrobial, tumor-inhibitory, anticoagulant, cardioactive, or neurophysiologic properties. Some of these substances have chemical structures that are unlike any compounds found in terrestrial species. These highly active compounds may serve as models in the development of new drugs.

It has been estimated that 7 to 10 years and a cost of over $5,000,000 are required to develop a new anticancer drug. This includes costs for the initial procurement of specimens, evaluation of crude extracts, purification, identification and synthesis of the active substance, pharmacological screening, clinical trials, and final Food and Drug Administration approval (*107*). But almost 20 years elapsed from the time that Bergmann identified arabinosyl nucleosides in a sponge to the time that cytosine arabinoside was developed and used clinically as an anticancer agent (*108*). Nereistoxin, first described in 1934, was not made into a marketable and effective insecticide until 1967. However, new developments in methods of extraction, physiological evaluation, structural determination, and chemical synthesis should shorten this process considerably.

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U.S. Universities and the World Food Problem

Inadequate funds still limit employment of U.S. scientists in developing countries despite remedial legislation.

Morris D. Whitaker and E. Boyd Wennergren

The production of food in the developing world is projected to increase at a substantially slower rate than the demand for food during the next decade and, in most countries, is not even expected to keep pace with growth in population (*1*). The growing deficit will require increasing dependence on food imports from the developed world where surpluses are forecast. However, many developing countries simply will not be able to export enough of their own goods to finance their food imports and will experience increased hunger and malnutrition, especially among their low-income masses. Furthermore, the deficit could be suddenly worsened in any year by universally poor weather which would result in outright starvation among relatively large segments of populations of the poorest countries.

Consequently, the problem of how to increase the rate of food production in the developing world is an urgent one. There is an emerging consensus that this will require, among other things, greatly increased investment in indigenous capacity for agricultural research which has been described as ". . . a critical

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