MARINE PHARMACOLOGY

A study of toxins and other biologically active substances of marine origin

Morris H. Baslow, Ph.D.

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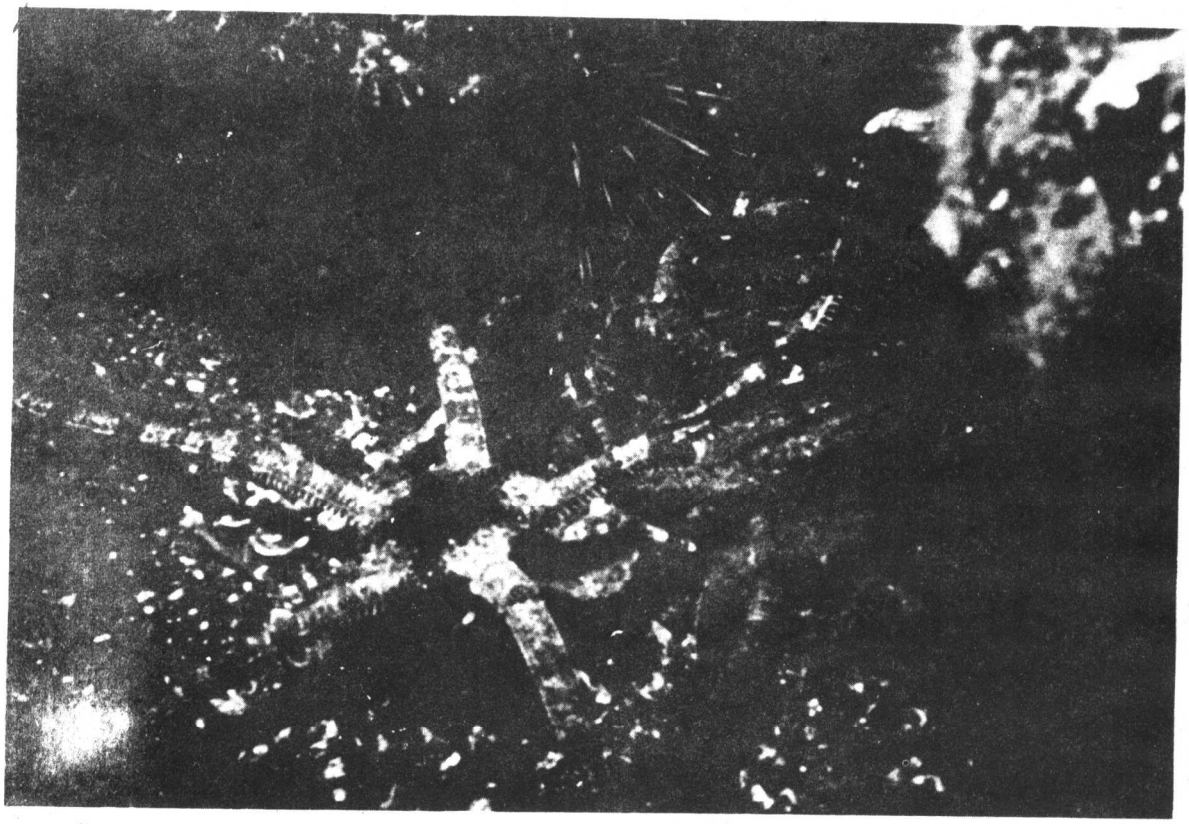

PLATE 1. Sea urchins and brittle stars off the coast of Santa Cruz Island, California at a depth of fifty feet. Photo by Kenneth Conklin

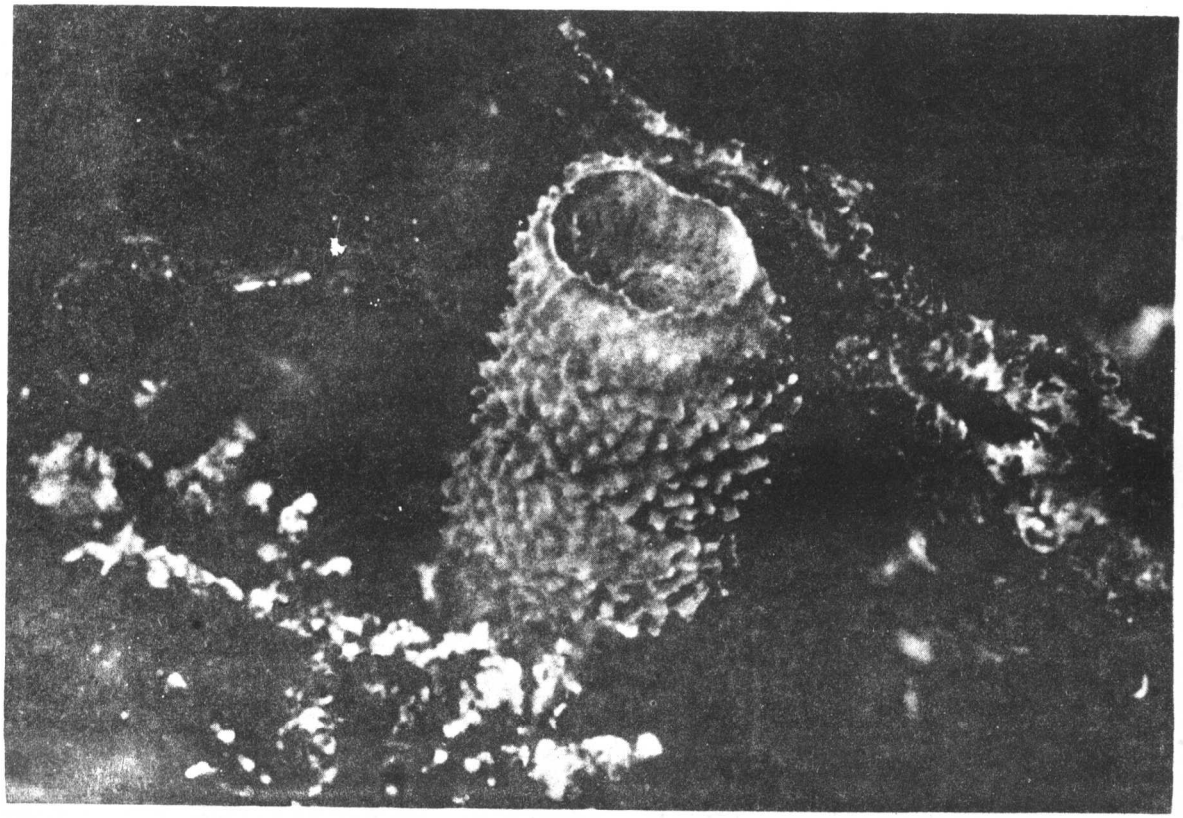

PLATE 2. The heavenly blue sponge *Dysidea etheria* in the Caribbean at a depth of approximately ten feet. Photo by Carleton Ray

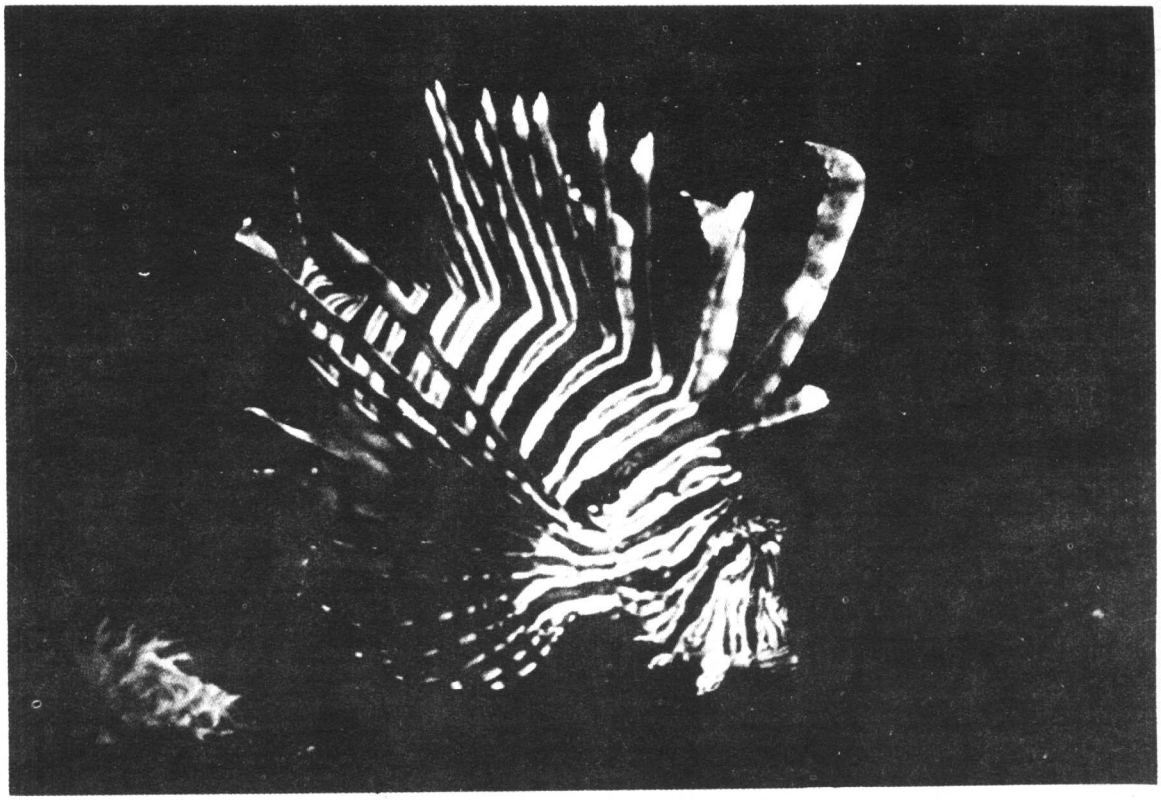

PLATE 3. An aquarium specimen of the lionfish *Pterois volitans*. Photo by Carleton Ray

PLATE 4. Reef fish among "horny corals" in the Caribbean at a depth of approximately twenty feet. Photo by Carleton Ray

PREFACE TO SECOND EDITION

This second printing of *Marine Pharmacology* has been produced in response to a continuing number of requests for the original text, now out of print, a demand this author finds very rewarding after the great initial effort that went into the preparation of this book.

Through the years, in discussions with researchers and students, the value of the text as a basic reference has been pointed out again and again. In fact, many who are actively engaged in this field find that the text grows more and more useful as its information content can be more fully exploited over a longer period of time.

On the other hand, like most other reference works of this nature, this book also had its failings. First, it is not an easy book to read. Secondly, the cost of the original hardcover "handbook" version was relatively high, thereby limiting its use by students. Finally, some readers found the subject index too abbreviated, while others decried the lack of an author index.

At first, I considered a revision of the text in which most of the above deficiencies might be addressed. However, on evaluating both the limited quantity of new material available at this time and the cost of such a revision, I concluded that several compromises would have to be made. Thus, it was decided that the most beneficial approach would be to reprint the original text, but to publish it in a paperback edition to reduce costs and to add a review chapter updating the text information to increase both its timeliness and its usefulness.

While the original text was designed primarily to be used by researchers as a handbook in the preparation of "active" substances for further biomedical investigations, it also contained a wealth of information on the systematics, biochemistry, toxicology, and biochemical interactions of marine organisms. This latter point was brought out by Kingsbury who, in his 1970 review of the text (Kingsbury, J. M., *Quart. Rev. Biol.*, June 1970), commented on the fact that marine bioactive substances ". . . owe their discovery to the obvious role they play in the ecological interrelationships of organisms."

Our present and limited knowledge of these bioactive substances certainly came from initial observations of easily discernable organism interactions. It follows that, although in most cases no definitive mechanism is known, natural perturbations of both long and short duration probably exist in the abundance of organisms; these are due in part to less obvious toxic, inhibitory, and stimulatory substances produced by almost all organisms and which affect others in the environment. In order to comprehend more fully the temporal makeup of aquatic communities, we must also understand how alteration in the abundance of one species can sometimes set off a devastating chain reaction in the environment. This sort of reaction has already been clearly documented in cases of the growth of toxic dinoflagellates and subsequent fish kill and shellfish poisoning episodes.

The study of these chemical interactions, in addition to providing better understanding and utilization of our marine resource, also will allow us to interpret the effects of human activity on the environment in a more meaningful way. Estimating man's impact, if any, on various aspects of our environment is an ex-

tremely difficult task. However, an understanding of the chemical mechanisms of organism interaction may very well tell us why a seemingly slight alteration has profound and longlasting effects on ecological processes, or, in other cases, may identify the cause of the observed perturbation as completely related to an independent, natural environmental fluctuation.

As we grow more and more dependent on the sea as a source of food and feedstuff, either through fishing or cultivation techniques, we must also understand both the food chain interactions and the variety of physiologically active and biotoxic substances present in new and unusual potential food organisms. The problem of "ciguatera" type intoxication as a result of eating normally nontoxic fish species is well documented. However, recent proposals that more exotic species be used for food as traditional species become scarce, and even that whole "fouling" communities be utilized as feedstock (Baslow, 1976, *Fourth Food-Drug From the Sea Conference,* Mayaguez, P.R.), must be thoroughly investigated in this regard.

It is hoped that this book will continue to stimulate research into the many aspects of biochemical control mechanisms among aquatic organisms, and that it will eventually lead to a better understanding and a more sensible approach to utilization of our aquatic environment.

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PREFACE TO ORIGINAL EDITION

This work is the outgrowth of the author's interest in marine pharmacology and biochemistry and of the presentation of a graduate course entitled "Marine Pharmacology" at the University of Hawaii for the past three years. As occurs in most rapidly expanding new scientific disciplines, there is no current text available which encompasses the field in its present embryonic state, and it is hoped that this effort will serve as the first stage in its consolidation.

The primary effort in this outline has been to bring together in a usable reference text the rapidly accumulating results of investigations into the pharmacological potential of compounds derived from marine organisms which are now scattered throughout the literature. I have tried to present in condensed form the present state of knowledge in each area and to give pertinent but not exhaustive references to the vast literature available. There are many excellent monographs and reviews of material on specific subjects, and in these the reader will be able to follow the development of past work in each field. In the present outline, all animal and plant phyla have been included, and all potential pharmacological agents have been considered. Non-marine organisms have been considered in a few cases in which it is probable that related marine forms contain similar substances. It is hoped that sufficient material has been included to make this text useful to those involved in biomedical studies of marine organisms.

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The author wishes to express his appreciation to the many members of the Department of Pharmacology, University of Hawaii Medical School, who spent long hours in discussion of relevant data during the preparation of this text. In addition, I am indebted to T. R. Norton, P. J. Scheuer, J. Randall, K. Gundersen, F. A. Kay and W. J. Newhouse of the University of Hawaii for their critical analyses of portions of the manuscript. The author assumes responsibility for what appears in this book. In a work of this nature there are bound to be errors of omission and commission, and suggestions and criticisms from the reader are invited.

I am also grateful to the many publishers who gave permission to use figures and tables from their books and to Margaret James and the secretarial staff of the Department of Pharmacology, who have been invaluable in the preparation of the manuscript.

Finally, I wish to express thanks to Windsor C. Cutting, Dean of the School of Medicine, without whose encouragement this task would never have been undertaken.

I would especially like to thank Dr. Ara DerMarderosian, Professor of Pharmacognosy, Philadelphia College of Pharmacy and Science, Philadelphia, Pennsylvania for his collaboration with and major contribution to the preparation of the update chapter of *Marine Pharmacology*.

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1 INTRODUCTION TO MARINE PHARMACOLOGY

The study of natural products which exhibit biological activity, derived from plants and animals, has long been of significant biomedical value, and crude products isolated from these organisms have served as a source of drugs and also of starting materials from which useful drugs could be synthesized.

In the case of antibiotics alone, substances which are produced by living organisms and which inhibit the growth or activity of other living organisms, more than 1,100 such substances have been described in the literature, and about 50 have found widespread use in the prevention and treatment of bacterial diseases in animals and man (Gale and Kiser, 1967). Progress in medicine has been greatly aided by these materials, and the search for new and better natural antibiotic and other drugs has not only continued but also increased in intensity. Today it is clear that most infectious diseases can be brought under control with natural or synthetic drug products, but with the subsequent increase in human longevity, new medical problems in the control of degenerative diseases have become of prime importance. We are still in great need of useful drugs that can inhibit viral infections and neoplastic growths, promote regeneration, aid in the treatment of cardiovascular degenerative processes and help to restore normal function in the aging nervous system. Studies of terrestrial organisms have proved to be most fruitful, and hundreds of clinically useful drugs with antibiotic, antitumor, cardiotropic and neurotropic activities have been added to our materia medica.

The wealth of materials that have been isolated from terrestrial organisms is in extreme contrast to the poverty of drugs that have been obtained from marine organisms.

Drugs from the Sea

The oceans and seas of the world cover approximately 71% of the earth's surface and include an abundance of organisms which, for the most part, are representatives of phyla present in the terrestrial and freshwater biospheres. There are some notable differences, however, in that only a very small number of vascular plant species, phylum Tracheophyta, are present in the sea, and some phyla, including the Echinodermata, have no non-marine forms. The question of why the sea has yielded a paucity of useful drugs must be considered in relation to the absence of marine Tracheophyta, which constitute a significant source of drug materials in the terrestrial environment, since a lack of useful starting materials may in part explain the slow development in this area. This appears not to be the case, however, and Emerson and Taft (1945), in considering pharmacologically active agents from marine sources in relation to the historical background of marine drugs and to medicinal agents found in marine organisms, concluded that "lack of application of substances from marine sources to medicine... is due more to lack of study of the highly potent agents available and search for others than to a paucity of pharmacologically interesting substances from the sea."

In several more recent reviews concern-

ing the potential of the sea as a source of pharmaceutical products (Schwimmer and Schwimmer, 1955; Halstead, 1957; Nigrelli, 1958; Burkholder, 1963; Endean, 1966; Nigrelli *et al.*, 1967; Burkholder, 1968; Halstead, 1968; der Marderosian, 1968, 1969), the presence of many interesting substances with biological activity isolated from marine organisms has been described, and similar conclusions have been reached. An organized effort to bring together many investigators and to consolidate this field was initiated within this decade, and the first symposium on the biochemistry and pharmacology of compounds derived from marine organisms was held in 1960 (Nigrelli, 1960). Since then, a number of reviews of the chemistry and pharmacology of marine toxins and other substances have appeared (Crescitelli and Geissman, 1962; Pax, 1962; Keegan and MacFarlane, 1963; De Clercq, 1964; Scheuer, 1964; Welsh, 1964; Russell, 1965; Halstead, 1965, 1967; Pourriot, 1966; Banner, 1967; Russell, 1967a, 1967b; Russell and Saunders, 1967; Lane, 1968; Cottrell and Laverack, 1968). Of these, the monograph of Russell (1965) and the treatises on poisonous and venomous marine animals of the world by Halstead (1965, 1967) have been most valuable. Articles dealing with marine pharmacology are scattered in the literature, although a survey of 551 selected articles indicates that about 75% appear in 48 journals (Table 1.1.).

Marine Pharmacology

The title selected for this text, *Marine Pharmacology*, or knowledge of drugs from the sea, must be accepted in its broadest sense at this time; by definition, this term means a branch of science that has to do with drugs from marine sources in all their relations. Marine pharmacology, as a biomedical discipline, involves the study of compounds derived from the sea and marine organisms that may be of medical value and is at present in its infancy. However, the growing awareness of the sea as a potential source of new drugs has been stimulated by recent studies which have pointed out agents effective against virus infections and certain tumors and by the elucidation of the chemical structures of several interesting neuroactive agents.

The study of marine pharmacology is important not only from the point of view of obtaining biomedically useful agents for the treatment of diseases. A second reason is that a better knowledge of the pharmacological effects of substances, especially toxins, from marine sources may result in more effective treatment of human or animal intoxications due to venoms or ingestion of toxic marine organisms. There has always been a limited problem of this nature, and we still have no effective treatments for intoxications due to sea snake venoms or ichthyosarcotoxins. Moreover, with the increased utilization of marine products as food materials, especially in preparations such as "fish flour" and in proposed algal products, in which substances formed by a number of diverse organisms may be included along with the major staple, there is a very real danger of mass intoxication of both an acute and an insidious nature. A better knowledge of marine pharmacology will enable us to prepare safer products.

In this work an attempt has been made to bring together a mass of data on toxins and other biologically active substances derived from marine organisms and to consider them in terms of their biomedical and pharmacological potential, although in most cases this was not the original concern of the investigators involved in this research.

Because of the recent and rapid proliferation of research in the area of marine natural products and the lack of adequate review of this field, there have been increasing instances of independent isolations of the same materials and confusion in the naming of these substances. The term "holothurin" has been given to steroid saponin fractions obtained from sea cucumbers by two researchers. Identical toxic fractions obtained from a sea snake have been named "erabutoxins" *a* and *b* and also "laticatoxins" III and IV, respectively, by other investigators. The elasmobranch oxytocin-like peptide hormones EOP I and E_2, isolated independently,

TABLE 1.1

The literature distribution of a selected list of citations which appear in this book. These comprise 551 articles, published in 163 journals between 1960 and 1968, which deal with aspects of marine pharmacology.

Journal	No. citations	% of total	Journal	No. citations	% of total
Science	44	8.0	Acta Pathol. Microbiol. Scand.	4	0.7
Ann. N. Y. Acad. Sci.	35	6.4	Agr. Biol. Chem.	4	0.7
Nature (London)	29	5.3	Arch. Int. Pharmacodyn. Thér.	4	0.7
Toxicon	27	4.9	Biochemistry	4	0.7
Amer. Zool.	23	4.2	Biochem. Pharmacol.	4	0.7
Gen. Comp. Endocrinol.	18	3.3	J. Physiol. (London)	4	0.7
Comp. Biochem. Physiol.	17	3.1	Limnol. Oceanogr.	4	0.7
Proc. Soc. Exp. Biol. Med.	17	3.1	Appl. Microbiol.	3	0.6
Biol. Bull.	16	2.9	Biochem. J.	3	0.6
Bull. Jap. Soc. Sci. Fish.	10	1.8	Biochim. Biophys. Acta	3	0.6
Experientia (Basel)	9	1.6	Can. J. Microbiol.	3	0.6
Fed. Proc.	9	1.6	C. R. Hebd. Séances Acad. Sci. Paris	3	0.6
Bot. Mar.	8	1.5	Develop. Biol.	3	0.6
Brit. J. Pharmacol. Chemother.	8	1.5	Helgolaender Wiss. Meeresunters.	3	0.6
J. Bacteriol.	7	1.3	Hawaii Med. J. Inter-Isl. Nurses Bull.	3	0.6
Tetrahedron Lett.	7	1.3	J. Amer. Chem. Soc.	3	0.6
Yakugaku Zasshi	7	1.3	J. Endocrinol.	3	0.6
J. Exp. Zool.	6	1.1	J. Gen. Microbiol.	3	0.6
Life Sci.	6	1.1	J. Gen. Physiol.	3	0.6
Toxicol. Appl. Pharmacol.	6	1.1	J. Neurophysiol.	3	0.6
Fish. Res. Board Can. J.	5	0.9	J. Pharmacol. Exp. Ther.	3	0.6
J. Pharm. Pharmacol.	5	0.9	J. Pharm. Sci.	3	0.6
Pac. Sci.	5	0.9	Tex. Rep. Biol. Med.	3	0.6
Proc. Nat. Acad. Sci. U. S. A.	5	0.9	26 Journals	2 (each)	9.5
Tetrahedron	5	0.9	89 Journals	1 (each)	16.1

may also be identical. There is also some evidence that the antiviral and antitumor fractions isolated from molluscs, designated "retine," "paolin 2" and "mercenine" by different investigators, may contain the same active components. Another problem in nomenclature has resulted from the isolation of different chemical entities which have been given the same trivial name. Such is the case for the sea hare toxin isolated from the digestive gland and a specific heterocyclic sesquiterpene bromocompound, both of which have been independently designated "aplysin." Holothurin B, a term originally used to designate cholesterol non-precipitable saponin components from the sea cucumber *Actinopyga agassizi*, has been used on two later occasions to designate two other components obtained from another sea cucumber, *Holothuria vagabunda*, which have different properties and empirical formulas from each other and which may also differ from the *A. agassizi* materials.

In the overall presentation of the data, the phylogenetic approach has been considered to be most useful. The classification system used in describing the groups dis-

TABLE 1.2

Classification of living organisms used in this text (Goodnight, Goodnight and Armacost, 1962; Meglitsch, 1967; Round, 1965; Pelczar and Reid, 1965).

- Plant Kingdom
  - Subkingdom Thallophyta
    - Phylum Schizophyta, the bacteria
    - Phylum Eumycophyta, the true fungi
      - Class Phycomycetae
      - Class Hyphochytridiomycetes
      - Class Oömycetes
      - Class Zygomycetes
      - Class Ascomycetae
      - Class Basidiomycetae
      - Class Dueteromycetes
    - Phylum Myxomycophyta, the slime molds
      - Class Myxomycetae
      - Class Plasmodiophoreae
      - Class Acrasieae
    - Phylum Cyanophyta, the blue-green algae
    - Phylum Euglenophyta, the euglenoids
    - Phylum Chlorophyta, the green algae
      - Class Charophyceae
      - Class Bryopsidophyceae
      - Class Conjugatophyceae
      - Class Oedogoniophyceae
      - Class Chlorophyceae
    - Phylum Chrysophyta
      - Class Xanthophyceae, the yellow-green algae
      - Class Chrysophyceae, the golden-brown algae
      - Class Haptophyceae, the golden-brown algae
      - Class Bacillariophyceae, the diatoms
    - Phylum Cryptophyta, cryptomonads
    - Phylum Pyrrophyta, the dinoflagellates
      - Class Desmophyceae
      - Class Dinophyceae
    - Phylum Phaeophyta, the brown algae
    - Phylum Rhodophyta, the red algae
  - Subkingdom Embryophyta
    - Phylum Bryophyta
      - Class Musci, the mosses
      - Class Hepaticae, the liverworts
      - Class Anthocerotae, the hornworts
    - Phylum Tracheophyta, the vascular plants
      - Class Psilophytineae, the psilophytes
      - Class Lycopodineae, the club mosses
      - Class Equisetineae, the horsetails
      - Class Filicineae, the ferns
      - Class Gymnospermae, the cycads, the conifers
      - Class Angiospermae, the flowering plants
- Animal Kingdom
  - Subkingdom Protozoa, acellular animals
    - Phylum Protozoa
      - Class Phytomastigophorea, plant-like flagellates
      - Class Zoomastigophorea, the colorless flagellates
      - Class Rhizopodea, rhizopods
      - Class Actinopodea, rhizopods
      - Class Telosporidea, sporozoans
      - Class Myxosporidea, sporozoans
      - Class Actinomyxidea, sporozoans
      - Class Microsporidea, sporozoans
      - Class Haplosporidea, sporozoans
      - Class Ciliata, ciliates
  - Subkingdom Metazoa, animals possessing many cells
    - Phylum Mesozoa, the mesozoans
    - Phylum Porifera
      - Class Calcarea, the calcareous sponges
      - Class Hexactinellida, the glass sponges
      - Class Demospongia, the horny or keratinous sponges
    - Phylum Cnidaria, the coelenterates
      - Class Hydrozoa, hydrozoans
      - Class Scyphozoa, the oceanic jellyfish
      - Class Anthozoa, the corals, sea anemones, sea fans and sea pens
    - Phylum Ctenophora, the comb jellies
      - Class Tentaculata
      - Class Nuda
    - Phylum Platyhelminthes
      - Class Turbellaria, free-living flatworms
      - Class Trematoda, parasitic flukes
      - Class Cestoda, parasitic tapeworms
    - Phylum Nemertina, the nemertean worms
    - Phylum Nematoda, the roundworms
    - Phylum Rotifera, the rotifers
      - Class Seisonacea
      - Class Bdelloidea
      - Class Monogononta
    - Phylum Gastrotricha, the gastrotrichs
    - Phylum Kinorhyncha, the kinorhynchids
    - Phylum Nematomorpha, hair worms
    - Phylum Acanthocephala, the thorny-headed worms
    - Phylum Entoprocta, the moss animals
    - Phylum Priapulida, the priapulids

TABLE 1.2—*Continued*

- Animal Kingdom—*Continued*
  - Phylum Annelida
    - Class Polychaeta, the polychaetes
    - Class Oligochaeta, the oligochaetes
    - Class Hirudinea, the leeches
  - Phylum Echiuroidea, the echiurids
  - Phylum Sipunculoidea, the peanut worms
  - Phylum Mollusca
    - Class Amphineura, the chitons
    - Class Scaphopoda, the tooth shells
    - Class Gastropoda, the snails, slugs and limpets
    - Class Pelecypoda, the clams, oysters, mussels and shipworms
    - Class Cephalopoda, squids, octopuses, nautiluses
    - Class Monoplacophora, chiton-like organisms
  - Phylum Ectoprocta, the bryozoans
    - Class Gymnolaemata
    - Class Phylactolaemata
  - Phylum Brachiopoda, the lamp shells
    - Class Inarticulata
    - Class Articulata
  - Phylum Tardigrada, the water bears
  - Phylum Onychophora, the onychophorans
  - Phylum Pentastomida, the parasitic pentastomids
  - Phylum Phoronida, the phoronids
  - Phylum Arthropoda
    - Class Pauropoda, myriapods
    - Class Symphyla, myriapods
    - Class Pycnogonida, the sea spiders
    - Class Crustacea, the crustaceans
    - Class Meristomata, the horseshoe crabs
    - Class Arachnida, the arachnids
    - Class Diplopoda, the millipedes
  - Phylum Arthropoda—*Continued*
    - Class Chilopoda, the centipedes
    - Class Insecta, the insects
  - Phylum Echinodermata
    - Class Asteroidea, the starfish
    - Class Ophiuroidea, the brittle stars
    - Class Echinoidea, the sea-urchins, heart urchins
    - Class Holothuroidea, the sea cucumber
    - Class Crinoidea, the sea lilies
  - Phylum Chaetognatha, the arrow worms
  - Phylum Pogonophora, the pogonophorans, the beard worms
  - Phylum Hemichordata
    - Class Enteropneusta, acorn worms
    - Class Pterobranchia, colonial forms
    - Class Planctosphaeroidea, known only from larvae
  - Phylum Chordata
    - Subphylum Urochordata
      - Class Larvacea, pelagic tunicates
      - Class Ascidiacea, ascidians
      - Class Thalliacea, tunicates with a transparent tunic
    - Subphylum Cephalochordata, the lancelets
    - Subphylum Vertebrata
      - Superclass Pisces
        - Class Agnatha, lampreys, hagfishes
        - Class Chondrichthyes, sharks, rays
        - Class Osteichthyes, bony fish
      - Superclass Tetrapoda
        - Class Amphibia, frogs, salamanders, toads
        - Class Reptilia, turtles, snakes, lizards, etc.
        - Class Aves, the birds
        - Class Mammalia, the mammals

cussed is presented in Table 1.2. Within a taxonomic grouping the materials of interest are discussed from the standpoint of function, and finally, functionally related materials within a taxonomic group are considered on the chemical level. In some cases similar or identical chemical constituents are found in more than one taxonomic group, and an attempt has been made to indicate these relationships.

The Future of Marine Biomedical Research

Although it is true that more than two decades after the observation of Emerson and Taft (1945) we have yet to harvest the pharmacological potential of the sea, recent interest in this area indicates that in the near future the oceans will yield biomedically important substances. National interest in this area has been stimulated, and biomedical applications of marine products have recently been considered by the President's science advisory committee on oceanography (Hornig, 1966), who concluded, "The great variety of plant and animal life in the sea offers abundant opportunities for study in many areas of biomedical research."

In hearings held by the House of Repre-

sentatives Subcommittee on Oceanography of the Committee on Merchant Marine and Fisheries to study implementation of the National Marine Sciences Program, the potential of obtaining drugs from the sea was considered. Dr. Leon Jacobs, Deputy Assistant Secretary for Science of the Department of Health, Education, and Welfare, concluded that "we have high hopes that the specific toxins and other substances to be isolated from marine life will be pharmacologically useful and that some of them may eventually have regular clinical uses . . ." (Jacobs, 1968).

Recently, Senator Warren G. Magnuson (Washington) introduced a bill, S. 2661, cosponsored by Senator Hiram L. Fong (Hawaii), to amend the Public Health Service Act to provide for the establishment of a National Institute of Marine Medicine and Pharmacology in the National Institutes of Health, the purpose of which would be to "establish in the Public Health Service an institute for the conduct of and support of research of the sea and its products with a view to advancing scientific knowledge which can be applied toward the causes, diagnosis, prevention, treatment, and control of physical and mental diseases and impairments of man" (Magnuson, 1967; Magnuson and Fong, 1967).

Academic awareness of the potential of this field has also been stimulated, and a series of biennial conferences on "Drugs from the Sea," sponsored by the Marine Technology Society and American Institue of Biological Sciences with support from the Office of Naval Research, have been initiated (Freudenthal, 1968). In addition, an outline for a new course in marine pharmacognosy has recently been proposed (der Marderosian, Youngken and Halstead, 1968).

This short text has been prepared with utility in mind, and it is hoped that it will be a useful aid in understanding the present state of the field of marine pharmacology. I have tried briefly to summarize the literature in several pertinent areas of research and indicate the most recent reviews in each subject in addition to discussing more recent work. Where practical, I have also tried to assess the pharmacological potential of the various natural products of marine origin.

Terrestrial organisms have yielded many biomedically useful substances; it is with high expectation that studies of marine organisms will prove to be just as fruitful. In addition, because of the differences in environmental conditions, it is possible that new or unusual biochemical entities have been evolved by marine organisms and that they exhibit biological activity. Since it is by analysis of the novel or unusual that advances in man's knowledge most often occur, it is hoped that studies of new and unique compounds derived from marine organisms will continue to increase our basic knowledge both of pharmacology and of medicine.

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