

Classification of Organisms

1. GENERAL

This introduction gives only a very general overview of the different organism types. The natural products with names given in **heavy type** are only typical representatives of those found. This is particularly true of the prolific groups such as cyanobacteria and sponges, where this introduction can only give general pointers and should not attempt to displace the function of the main body of the Dictionary. To obtain a more comprehensive overview of the natural products present in particular types of organism, it is necessary either (a) to browse the entries given in the main section of the book, or (b) to search the CD-ROM version. This is most effectively done by using the **Type of Organism codes**, which are given in each section below (and above). These can be used alone or combined with other types of search parameter to restrict the result to certain broad classes of organism.

Many natural products pass up the food chain, and what may have been isolated for example from a sponge, may in fact be a cyanobacterial metabolite. This phenomenon reflects the large range of signalling roles (in the widest sense, to include defence chemical and anti-predator substances) that the marine environment involves, and the complexity of the alimentary chains which leads to frequent metabolic modification of molecules taken up from prey organisms.

Wherever possible, the Dictionary carries codes for both types of organism in the entry, but this cannot always be guaranteed. Other marine natural products such as the commoner steroids are just widespread, not necessarily as part of the food-chain.

Kornprobst, J.-M. (ed.), *Substances Naturelles d'Origine Marine*, Lavoisier, Paris, 2005

This recent two-volume work gives much background information on all aspects of marine natural products, including more detailed schemes for correlation of natural product type with taxonomic position of the organism. It was consulted extensively in preparing this introduction.

Tringali, C. (ed.), *Bioactive Compounds from Natural Sources*, Taylor & Francis, 2001

2. TAXONOMIC CONSIDERATIONS

The nineteenth century high-level classification of organisms into plant and animal kingdoms has been abandoned since about the 1960s with the development of cladistic analysis. Since then it has become increasingly clear that certain groups of organisms, some of them previously little studied, such as the cyanobacteria or cyanophytes (so-called blue-green algae; more closely related to bacteria), the chromista (including the brown algae) and the archaeobacteria or archaea, show greater differences in both fundamental biochemistry and genetics from each other and from the so-called higher organisms, than higher plants and animals show from each other. Whittaker (1959) proposed that the most fundamental division should be between the prokaryotes and the eukaryotes, a classification that has now been generally accepted, but subsequently modified to include the discovery of the archaea in the 1970s.

Further studies of the genome might in principle lead to a classification scheme of all organisms that can be considered 'absolute', but many ecologists consider this view as essentially simplistic; for example, it does not take into account the possibility of convergent evolution in the genome. Evolutionary pressures are exerted through the phenotype, not the genotype.

Genus names in this Dictionary have, wherever possible, been validated using the *Species 2000/ITIS Catalogue of Life*, with which the Chapman & Hall/CRC chemical database has established a reciprocal relationship. The Catalogue of Life (COL) must be considered the most authoritative resource across the whole of taxonomy in respect of taxa which it currently covers. COL is a cooperative integration and standardisation of the information contained in many of the world's authoritative databases. At the time of finalisation of the dataset for this Dictionary, COL gave a taxonomic view of over half the world's reported species, and is planned to achieve completion in terms of published taxa by 2011. Where the name reported in the primary literature is not yet in COL, the genus name was cross-checked with other internet resources. If a genus name appears unreliable, this is noted in the entry.

There are many different schemes for taxonomic higher-level organisation. The discussion which follows is largely based on schemes given in Kornprobst (2005). Users should be aware, however, that the classification of genera into phyla, classes, subclasses, etc. given in Kornprobst is only one view. In some groups of organism (e.g. molluscs) there is reasonable agreement among biologists; in others (e.g. protozoa) there are huge differences between different schemes. Since most users of this Dictionary are likely to want to search using broad parameters (e.g. 'Find all pyridines in echinoderms', 'find all compounds with MW 300-310 in ascomycetes'), the Type of Organism categories have been kept broad, (largely phyla) and the uncertainties concerning organisation between the level of phylum and the level of genus should not affect the results. Where there are major taxonomic uncertainties, as with protozoa, the phylum is not subdivided; all organisms that can reasonably be considered as protozoa are grouped under the same code heading (**ZD**). Future development of the database may involve some further subdivision of these large categories.

Whittaker, R.H., *Quart. Rev. Biol.*, 1959, **34**, 210–226 (*organism classification*)

Cimino, G. *et al*, *Marine Chemical Ecology*, (eds. McClintock, J.B. *et al*), CRC Press, Boca Raton, 2001, **115** (*rev, taxonomy*)

2.1 ARCHAEA (Archaeobacteria) (ZA)

The archaea are prokaryotic organisms inhabiting extreme environments, both marine and terrestrial, such as hydrothermal vents, and also highly saline regions. There are three generally recognised groups; thermophiles (heat-tolerant), halophiles (tolerant of highly saline media such as the Dead Sea; some species are also extremely alkali tolerant, growing in media up to pH 12) and methanogens (some species of which are also highly thermotolerant). It is also convenient to recognise a group of 'psychrophiles' tolerant of cold arctic and antarctic conditions. Although only discovered in the 1970s, it now appears that the archaea are in fact the most numerous bacteria in the marine environment. They show major differences from other prokaryotes in their genome, and these are carried through into fundamental differences in their membrane structure and biochemistry. Their cell walls do not contain the glycopeptides found in the eubacteria. Stabilisation of the membrane structure is affected by esters of glycerol with characteristic branched-chain terpenoid fatty acids, a role which in prokaryotes is performed by carotenoids and/or hopanoids and in eukaryotes by sterols. **Archaeol** is considered the prototype of this type of lipid; there are some unusual structural variations; for example the presence of lipids based on **Calditol** is noteworthy. A number of prenylated naphthoquinones related to vitamin K₁ have also been isolated, and sulfur bacteria contain a range of prenylated and aliphatic sulfur compounds.

2.2 EUBACTERIA (ZB)

The eubacteria are characterised by their cell wall structure, which is based on a glycoprotein formed of (1 → 4) linked *N*-acetylglucosamine and *N*-acetylmuramic acid, cross-linked by peptide side chains containing unusual amino acids which render different bacterial strains biochemically and immunologically distinct. In Gram-positive bacteria the glycoprotein coat forms the outermost layer; in Gram-negative bacteria there is an outer membrane coat which prevents this layer being stained by the reagent.

The classification of bacteria is a complex and specialised subject, and there is no official classification scheme. The nearest equivalent is the scheme being evolved for Bergey's Manual (Garrity *et al*), which is work in progress available for inspection online.

Bacteria may be photosynthetic or nonphotosynthetic, and the photosynthetic bacteria may be anaerobic (sulfur bacteria) or aerobic (which includes the cyanobacteria). The former group utilises the bacteriochlorophylls as photosynthetic pigments. Further major subdivisions such as alpha, beta-, gamma- and deltaproteobacteria have been delineated according to various schemes, but the overall picture is complex. Fortunately, within the context of natural products, the majority of investigations have been into two major bacterial subcategories, the actinomycetes and the cyanobacteria. The code ZB0001 is used in this Dictionary for all eubacteria which do not fall into one of these two major groups.

It is possible that some isolations from eubacteria, including actinomycetes, that have not been prominently flagged in the literature as being of marine origin, do not appear in this Dictionary. To search all bacterial isolations, consult the Dictionary of Natural Products on DVD. The coverage of cyanophyte products should be complete.

- Lepage, S.P. *et al*, *International Code of Nomenclature of Bacteria*, American Soc. for Microbiol, Washington D.C., 1992
- Austin, B., *Recent Advances in Marine Biotechnology*, (eds. Fingerman, N. *et al*), Science Publishers, USA, 2001, **Vol. 6**, 1–28 (rev)
- Piel, J., *Nat. Prod. Rep.*, 2004, **21**, 519–538 (rev, *symbiotic bacteria*)
- Garrity, G.M. *et al*, *Taxonomic Outline of the Prokaryotes, Bergey's Manual of Systematic Bacteriology*, 2nd edn, version 5.0, May 2004 http://141.150.157.80/bergeysoutline/outline/bergeysoutline_5_2004.pdf
- Moore, B.S., *Nat. Prod. Rep.*, 2005, **22**, 580–593 (rev)
- König, G.M. *et al*, *ChemBioChem*, 2006, **7**, 229–238 (rev, *natural products from associated microbes*)

2.3 CYANOBACTERIA (ZB1000) (cyanophytes, blue-green algae, Myxophyceae)

The older term blue-green alga is now considered a misnomer, and the cyanobacteria are considered a subdivision of the photosynthetic eubacteria. They are unicellular organisms which are both marine and terrestrial; some marine species also inhabit fresh water. Some are truly monocellular, but when found unassociated with other organisms, many species adhere via their mucilaginous coats into filaments or tufts visible to the naked eye, and are sometimes found as large colonies known as stromatolites. These are well documented in the precambrian fossil record and thus place the cyanobacteria among the earliest known organisms. Schemes for the subclassification of cyanobacteria are based on their mode and degree of such association, or alternatively by the type of spores formed. Attempts have also been made to classify them chemotaxonomically. About 7500 species have currently been described. According to one view as few as 200 of these may be taxonomically distinct, but conversely according to recent chemical studies, a colony appearing to consist of a single species may comprise many genetically distinct strains. Cyanobacteria are responsible for frequent algal blooms, the toxicity of which is associated with their high level of secondary metabolites.

Their cell wall structures contain some sterols, but more characteristically conjugated hopanoids such as **Bacteriohopanetetrol**. The fundamental chemotaxonomic distinction between prochlorophytes and cyanobacteria lies in their photosynthetic pigments; in cyanobacteria there is **Chlorophyll a** but no chlorophyll b, which is replaced by the phycobilins, **Phycoerythrobilin** and **Phycocyanobilin**. These pigments are also found in the red algae, which show other chemical similarities to the cyanobacteria, notably in their polysaccharides. Cyanobacteria contain characteristic xanthophylls such as **Myxoxanthophyll**.

Cyanobacteria are present in the tissues of many sponges, often as a major component of the biomass. In an extreme case, the species *Terpios hoshinota* has been characterised as a 'Cyanobacteriosponge', in which the cyanobacterial cell mass constitutes over 50%. Some of the sponge-associated cyanobacteria are of unique type and have even been assigned to new genera. DNA sequence analysis has shown that different species of *Dysidea* sponge are associated with a different cyanobacterium, which may account for the wide range of different secondary metabolites isolated from them, while mass spectral analysis of colonies of *Microcystis* and *Planktothrix* cyanobacteria has demonstrated the presence in a single colony of multiple strains showing great diversity in their metabolites. Attempts to separately culture these cyanobacterial cells have proved unsuccessful, and evidence as to the true origin of the secondary metabolites is based on cell separation experiments. Peptides such as **13-Demethylisodysidenin** and chlorinated diketopiperazines, such as **Dihydrodysamide C**, were exclusively found in the cyanobacterial cells, whereas several terpenoids, such as **Spirodysin**, were found in the sponge cells. Halogenated aromatics are also associated with the cyanobacterial fraction of *Dysidea* sponges, and resemble metabolites such as **Ambigols** from cultured cyanobacteria.

The most characteristic secondary metabolites of the cyanobacteria, free or associated, however, are nitrogenous. The known metabolites are also characterised by a high degree of halogenation. See for example the extensive series of **Malýngamides**. A high degree of halogenation (notably terminal -CCl₃ groups) is shown by **Dysidenin** and its relatives isolated from sponge-cyanobacterial symbionts. An extensive series of brominated indoles typified by the **Hapalindoles** have been isolated.

Cyanobacteria produce an extensive range of modified depsipeptides, largely cyclic. Examples include the **Lyngbyabellins** and **Majusculamide C**. Acyclic peptides include the **Tasiamides** and the **Microcolins**.

- Burja, A.M. *et al*, *Tetrahedron*, 2001, **57**, 9347–9377 (rev)
- Gerwick, W.H. *et al*, *Alkaloids*, 2001, **57**, 75–184 (rev)
- Van Wagoner, R.M. *et al*, *Adv. Appl. Microbiol.*, 2007, **61**, 89–217 (rev)

2.4 ACTINOMYCETES (ZB5000)

These are a particular class of Gram-positive eubacteria showing filamentous growth, and some similarities to fungi. (In the past they have often been classified as filamentous fungi and are sometimes called 'higher bacteria'). They also merit special treatment biochemically speaking because of their vast production of different types of natural product, many of them with strong antibiotic or other pharmacological activity. The most important genera by far in terms of natural products are *Streptomyces* and *Actinomyces*; according to which definition is used, the actinomycetes can also include the important pathogenic genera *Nocardia* and *Mycobacterium*.

Actinomycetes occur in marine sediments, and probably as endophytes in many marine organisms, but evidence is fragmentary. As a group they tolerate a wide range of salinities. A typical situation is that of the indolocarbazole alkaloids (VX4350), the Staurosporines. Staurosporine itself is produced by various actinomycetes, both terrestrial and marine, but close homologues have been obtained from ascidians *Eudistoma*, from planarians *Pseudoceros* that prey on them, and from prosobranch molluscs *Coriocella*. The Holyrines, isolated from actinomycetes present in marine sediments, are probable precursors of these compounds and support the idea that they are all of ultimate actinomycete origin.

Moore, B.S., *Nat. Prod. Rep.*, 2005, **22**, 580–593 (*microorganism biosynth*)

König, G.M. *et al*, *ChemBioChem*, 2006, **7**, 229–238 (*rev, natural products from associated microbes*)

2.5 PROTOZOA (ZD)

The term 'protozoa' is difficult to define taxonomically and is subject to ongoing modification in the light of biochemical studies, which are leading to the reclassification of many groups. It was formerly used as a blanket term to describe almost any kind of unicellular organism, but it is now known, for example, that the dinoflagellates (see ZH7000) are more closely related to the brown algae than to other unicellular organisms. In this Dictionary the code ZD0001 is used for all unicellular organisms that cannot be placed elsewhere*. The ciliate organisms, for example *Paramecium*, can be placed here, although it now appears that they are biochemically closest to the dinoflagellates. It is convenient to recognise four subdivisions; flagellates, amoebae, sporozoans and ciliates, but the reservations expressed above concerning their fundamental dissimilarities must be borne in mind, and a proper classification remains premature. Genera studied chemically include *Euplotes*, *Tetrahymena*, *Litonotus* and *Pseudokeronopsis*. The ciliates are nonphotosynthetic organisms but can often harbour photosynthetic algae as symbionts.

Chemical studies have been fairly limited, but a range of sesquiterpenoids, and some highly unusual triterpenes, the **Vannusals**, have been isolated.

* Some genera considered dinoflagellates are currently classified in the Dictionary under ZD0001, protozoa, but they are being reclassified under dinoflagellates, ZH7000, for future releases of the database

3. MARINE ALGAE; GENERAL CONSIDERATIONS

The algae considered in their totality, can be described as lower, mostly multicellular plants of a simple body plan, lacking well-defined differentiation into roots, stems and leaves. The higher plants, which show such differentiation, are virtually absent from the oceans, although some species (mangroves; several different spp. of higher plant) are important components of the estuarine saltmarsh environment.

The classification of algae has undergone a number of changes in recent decades and there is no definitive overall plan that takes care of every subgroup. The most fundamental division is between the Brown algal branch and the Green algal branch, two groupings which show large biochemical differences from each other. The 'Green' branch comprises not only the green algae proper (Chlorophyta), but also the red algae (Rhodophyta), which are now considered more closely related to the green algae than either of them are to the brown algae and their relatives. The taxonomic classification codes used here recognise only these major subdivisions, although one scheme for the Chlorophyta for example subdivides them into fourteen orders.

Red and brown algae are of commercial significance, but the commercial exploitation of green algae is very limited. The use of whole plants as food products is mostly confined to Japan, but the extraction of the algal polysaccharides for use in food and medicines is a major industry.

3.1 CHLOROPHYTA (green algae) (ZE)

About 7000 species are recognised, of which 1000 are marine, inhabiting mostly surface waters of the calmer seas. Of these, about 20% have so far been investigated chemically, principally in the orders Broopsidales and Ulvales. In their fundamental biochemistry (photosynthetic pigments, storage polysaccharides etc.) they resemble the higher plants. Some members are unicellular, sometimes as endophytes in other species of green algae.

Green algae photosynthesise using the common carotenoids α - and β -Carotenes, and contain a range of relatively common xanthophylls such as **Lutein**. The most common storage polysaccharides are amylose and amylopectin, and the commonest structural polysaccharide is cellulose, although some groups also secrete β -1,3-xylan and β -1,4-mannan. The most widespread sterols are Cholesterol, Brassicasterol, Sitosterol and their close relatives, although some rarer sterols such as **Saringosterol** have been characterised from certain classes of green algae. Studies have not always distinguished between sterols involved in the algal membrane structure and those present in the cytoplasm.

The known secondary metabolites of the green algae are rather limited in structural range and are mostly confined to terpenoids of relatively common skeleton, and a range of aromatics including meroterpenoids. Halogenation is uncommon, and the terpenoids are so far limited to sesqui- and diterpenes and a few triterpenes (acyclic and pentacyclic cycloartanes, e.g. **Capisterone B**). Many of the terpenoids contain enoloid functionality, for example **Caulerpenyne** and/or furan rings formed biogenetically by the cyclisation of the related unsaturated aldehydes, such as **Furocaulterpin**. Some of these metabolites have also been isolated from species that feed on green algae, such as molluscs. **Halimedatriol** is the only terpenoid so far isolated from green algae containing a carbon skeleton that has not been found elsewhere. The brominated aromatics are exemplified by **Rawsonol**, and the meroterpenoids by **Cymopol** and related compounds.

Nitrogenous compounds found in green algae tend to be low molecular-weight amines related to the amino acids, such as Agmatine, or peptides and modified peptides such as the **Kahalalides**. There are few more highly elaborated alkaloids except for purines and an unusual 1,3,5-triazine, **Halimedin**. Exceptions to this generalisation are the five-ring nitrogenous pigments **Caulerpin** and **Caulersin** isolated from the structurally atypical algae of the *Caulerpa* genus.

3.2 RHODOPHYTA (red algae) (ZF)

The red algae are characterised by a unique and complex reproductive cycle involving three alternating generations. The great majority of the 4000 species known are marine, sometimes inhabiting deep water. They may be mono- or multicellular with a complete absence of flagellae. The chloroplasts have a double membrane similar to those of cyanobacteria and presumably arose by endosymbiosis with these organisms. There is no general agreement about the subclassification of red algae. Several schemes have been suggested, and the taxonomy is fluid, for example the genus *Plocamium* has now been moved to a separate order, the Plocamiales. At the highest level, a division into two unequal subclasses is usually recognised. The Bangiophyceae, considered the more primitive group, is the smaller and consists of either unicellular or very simple multicellular organisms. The most studied genus chemically in the Bangiophyceae is *Porphyra*. The larger subgroup is the Florideophyceae, comprising the better-known more highly differentiated macroscopic plants.

An important biochemical similarity between the red algae and the cyanobacteria is the presence of the phycobilins, **Phycocyanobilin** (blue-green) and **Phycoerythrobilin** (red). It is the latter that is responsible for the red colour of the tissues, but the colour may be modified or masked by the presence of phycocyanobilin and/or chlorophylls. The red algae contain chlorophyll a and the characteristic pigment **Chlorophyll d**. The isolation of **Isochlorin e₄** from *Dasya pedicellata* is also noteworthy. The range of carotenoids is rather limited but includes the furanoid cyclised xanthophylls **Aurochrome** and **Auroxanthin** which are also widespread in terrestrial plants.

The storage saccharides consist not only of highly branched amylopectins but of the osmoregulatory galactoglycerols **Floridoside** and **Isofloridoside**. There is some cellulose content but the most abundant and characteristic polysaccharides are the commercially significant **Carrageenan** and **Agar**. These are rarely present in the same species. Red algae have a relatively high content of polyunsaturated fatty acids and phospholipids, as well as some unusual acids such as the cyclopentanoid **Dihydrochaulmoogric acid**. Derived from these unsaturated C₁₈ and C₂₀ acids are a large number of oxylipins, for example the **Constanolactones** and **Peyssonenyne**s. The range of sterols so far characterised is rather narrow and confined to relatively simple hydroxylated cholestanes such as the **Liagosterols** and **Pinnasterol**. Side-chain methylated steroids are rare; see **11,20-Dihydroxy-23-methylcholesta-1,22-dien-7-one**.

The secondary metabolites of the red algae are characterised by a high proportion of halogenated terpenoids and aromatics, particularly in the intensively studied genus *Laurencia*. The terpene skeletons are strongly

weighted towards the lower MW members of the series (especially sesquiterpenes), and there are many representatives of unique terpene skeletons not found in higher plants or elsewhere in the algae. Kornprobst [Kornprobst, 2005; **1**, 329] attempts a correlation of natural products with taxonomic subgroup (order), but in view of the taxonomic uncertainties referred to above and to the fact that several groups have hardly been investigated chemically, this must be considered tentative; the classification of red algae into orders given by Kornprobst and given here does not correspond with that found in the Catalogue of Life. The Ceramiales (e.g. *Ceramium*, *Delesseria*, *Chondria*, *Laurencia*, *Polysiphonia*) contain many halogenated sesquiterpenes and brominated aromatics, plus a range of halogenated C₁₅ acetogenins which are characteristic of the order. The Gigartinales (e.g. *Chondrococcus*, *Plocamium*, *Ochtodes*, *Sphaerococcus*) also contain many halogenated terpenes, mostly monoterpenes such as **Halomon** and **Violacene** but in the case of *Sphaerococcus* some (often brominated) diterpenes based on sphaerane, presphaerane and related carbon skeletons, such as **Sphaerococcenol A** and **Presphaerol**. On the other hand, the Nemaliales (e.g. *Asparagopsis*, *Bonnemaisonia*, *Rhodymenia*) and others yield halogenated aliphatic compounds of low molecular weight such as halogenated acetones. The genus *Ochtodes* (Cryptonemiales) yielded a range of halogenated monoterpenoids based on the unusual ochtodane skeleton, such as **Ochtodene**; other genera in this order did not contain terpenoids. Other orders have either not been extensively investigated, or yielded only a limited range of natural products.

The order Ceramiales, especially the genus *Laurencia*, is a rich source of natural products with over 500 compounds so far isolated. The sesquiterpenes of *Laurencia* are based on more than 20 different carbon skeletons, some of them 'traditional' and found also in terrestrial organisms, others novel. Many of these have also been isolated from molluscs and other animals that feed on red algae. Using chemotaxonomic evidence, the species in this genus can in fact be divided into three subgenera. The first group contains only halogenated terpenes, the second only acetogenins and the third group both. However, the situation is complex and there may be interbreeding between different chemotypes. [Kornprobst 2005; **1**, 346–347]. There is also a wide range of halogenated (mostly brominated) diterpenes, many derived from the common (marine and terrestrial) skeleton labdane and other skeletons closely related to it. The parguerane skeleton, as found in **Parguerene** and related compounds, is however unique to marine organisms. There is also a series of **Irieols** based on the irieane skeleton. Certain *Laurencia* and *Chondria* species have also yielded a series of triterpenoid polyethers derived from squalene, for example **Thyrsiferol**, **Enshuol** and the **Armatols**.

The most characteristic class of natural product isolated from these genera, however, is the extensive series of mostly halogenated compounds based on a linear C₁₅ skeleton, the first of which to be discovered was **Laurencin** in 1968. A wide variety of structure based on ether formations is founded on this basic skeleton (for example **Obtusenyne**; **Microcladallenes**), which probably arise by loss of a C₁ fragment from a C₁₆ precursor. The isolation of **Laurediol** supports this hypothesis. The Ceramiales also contain a range of halogenated phenolics such as **Lanosol**.

Nitrogenous natural products are relatively scarce in the majority of red algae, and mostly limited to widely-distributed small molecules such as **Homarine**, and cyclic peptides such as **Ceratospongamide** (isolated from a red algal-sponge symbiont). A range of simple halogenated indoles was isolated from *Rhodophyllis membranacea*. Once again, it is the Ceramiales that show a much greater range. A characteristic amino acid is **Kainic acid**, together with its homologue **Domoic acid** and other analogues. The range of indoloids is also greater, including some of greater elaboration such as the **Almazoles**.

The chemotaxonomic unpredictability of this group of organisms is shown by studies of *Chondria californica*, which yielded a range of polysulfur compounds such as **Lenthionine**. These were unaccompanied by terpenes, and were not found in apparently closely related species.

3.3 PHAEOPHYTA (brown algae) (ZH1000)

About 1500 species of brown algae are known, almost exclusively marine. The term Phaeophyta is to be preferred, since modern studies have shown that they are only very distantly related to the other algae and the term 'brown alga' is therefore a misnomer, although it remains in widespread use. Together with the diatoms and the chrysophytes, they constitute the Stramenopiles. Whereas the other two subgroups are entirely unicellular, the vast majority of brown algae are multicellular and macroscopic, sometimes attaining very large size. Most species inhabit cold and temperate, often rough, seas, and are sessile, demonstrating a well-defined differentiation into a foot (holdfast), stem (stipe) and frond, and growing in surface or relatively shallow waters. The exception is the brown algae of the Sargasso Sea, which are two free-floating *Sargassum* species inhabiting tropical waters.

Two superorders are recognised, based on life-cycle criteria. The Fucales do not show generational alternation, producing haploid gametes which reproduce the diploid stage (cf. higher plants and animals). The other brown algae show generational alternation between a haploid gametophyte and a diploid sporophyte (cf.

ferns). In some families the two forms are both macroscopic and may be indistinguishable to the naked eye; in others, the gametophyte is microscopic. Kornprobst [Kornprobst, 2005; **1**, 420–421; *ibid.*, 481] gives a classification scheme into 11 orders (the Fucales being one), but as with the red algae, there have been several different views of the taxonomy in recent years, with much ongoing research having chemotaxonomic implications. For example, it has been shown that the much-studied *Dictyota dichotoma* must be considered a complex in which several endophytic species can be distinguished.

The photosynthetic pigments of all organisms of the Stramenopiles are **Chlorophylls a, c₁ and c₂** (characteristic absence of chlorophyll b). The carotenoid content is limited to **Fucoxanthin** and lesser amounts of **Violaxanthin**, **Diatoxanthin** and **Diadinoxanthins** have also been reported, but may be the result of diatomaceous contamination of samples. Some Fucales have yielded pseudomonoterpenoids related to **Loliolide**, which in other types of organism are known to be degradation products of xanthophylls.

Both the structural and the storage carbohydrates of the phaeophytes differ from those present in other classes of algae. The main storage polysaccharide is **Laminarin**, accompanied by **Mannitol** and **Laminitol** which perform osmoregulatory functions. The matrix polysaccharides are based on **Alginic acid** in which the anions are carboxylate groups rather than the sulfates found in carageenans and agar. Phaeophytes in the orders Fucales and Laminariales also contain smaller amounts of the pharmacologically interesting **Fucoidin**.

As in the red algae, the range of sterols found is limited and mostly based on minor modifications of the **Fucosterol** structure, which is the major steroid. There is a wide range of unusual oxylipins, for example the rare oxa compounds given in the entry for **12-Hydroxy-6,9,11-dodecatricenoic acid**, bridged epoxy compounds such as the **Cymathere ethers**, and prostanoid-like cyclopentanoids such as the **Ecklonialactones**.

Brown algae contain a wide range of terpenoids, phenolics and meroterpenoids, but a striking and somewhat unexpected feature is the paucity of halogenated compounds, and those that are found in small amounts are bromo- and iodo-, rather than chloro-substituted. They are unique in their ability to concentrate iodine (and also arsenic; see below) to concentrations of up to 1% dry weight, and although 99% of the iodine in the tissues is inorganic, the other 1% finds its way into **Thyroxine** and other iodinated tyrosines, and a small number of miscellaneous phenolics. There are also few alkaloids, nitrogen compounds being represented only by compounds of low molecular weight, some peptides such as **Fastigiatine** and one or two other compounds such as the terpenoid amide **Joalin**. However, studies have so far been confined to two orders, the commercially important Fucales and the Dictyotales. No lower terpenoids have been isolated from the former group, and mostly only linear diterpenes such as **Crinitol**, although the presence of the rare cyclobutanoid norditerpene **1-(2-Isopropyl-1-methylcyclobutyl)-4-methyl-4-nonene-1,8-dione** in *Cystophora moniliformis* is noteworthy. On the other hand the Dictyotales contain some sesquiterpenes such as **Zonarene**.

The diterpenoids of the Dictyotales include many examples of prenylogues of well-known sesquiterpenoid skeletons, for example **Dilophol** (prenylgermacrane), **Dictyotin A** (prenylcadinane = biflorane) **Dictyotetraene** (a dictyotane) and other elaborations on this theme (for a tabulation in chart form, see Kornprobst, 2005, **1**, 442-3). Other characteristic skeletons are xenicane and its relatives (pachydictyane, crenulane and others), and dolabellane and dolastane.

The major secondary metabolite content of brown algae is represented by phenols and phenolic meroterpenoids, many of them sulfated and/or halogenated. The content of these in the tissues may reach 20% by weight and they may play a role in the prevention of larval fixation by marine animals and for protection against bacteria. A major series is represented by the phlorotannins (see for example **Trifucol**, **Trifuhalols**, **Eckol** and their numerous homologues) which are radical-induced oligomers of Phlorotannin containing C-C or C-O-C linkages. The genus *Cytoseira* has been much investigated and has yielded a large range of structurally diverse meroterpenoids; for example, **Strictaketol**, the **Cystoseirols** and the **Mediterraneols**.

The reproductive cycle of brown algae is mediated by a range of hydrocarbon pheromones secreted by the female gametes, and which act as attractants for the male cells. In some orders of brown algae the gametes are both mobile and may be either of similar (microscopic) size, or with the female gamete larger. The most advanced form of reproduction is shown by the Fucales, where the female gamete is large and immobile, and the male gamete is attracted to it solely by the very low concentrations (nanomolar to picomolar) of the attractants. These molecules modulate the navigation of the male gametophytes in the marine environment over the very short ranges (~1mm) required for fertilisation. They are small, non-halogenated aliphatic molecules, the secretion of which is a unique feature of phaeophyte biochemistry. The majority are C₁₁ compounds which appear to be derived by degradation of unsaturated acids such as eicosahexaenoic, of a type not found in terrestrial plants. They may be acyclic (e.g. **Cystophorene**) or containing 3-, 5-, 6-, 7- or 8-membered rings (e.g. **Dictyopterenes A-B**, **Multifidene**, **Aucantene**, **Ectocarpene** and **7-(1-Propenyl)-1,4-cyclooctadiene** respectively). Some *Fucus* and

Sargassum species employ the smaller molecule **1,3,5-Octatriene** (various stereoisomers). Unexpectedly, Ectocarpene was also found in terrestrial *Senecio* spp.

The tissues of brown algae uniquely concentrate inorganic arsenic at concentrations of up to 40ppm and some of this is converted via biomethylation to dimethylarsinate and thence into a range of ribosides such as **2,3-Dihydroxypropyl[5-deoxy-5-(dimethylarsino)]ribofuranoside**.

3.4 BACILLARIOPHYTES (diatoms), CHRYSOPHYTES (golden algae) and HAPTOPHYTES (ZH5000)

These three groups of unicellular organisms belong to the 'brown' major biochemical line and together with the brown algae (mostly multicellular) constitute the Stramenopiles. The term 'algae' formerly applied to some of these groups is now considered on biochemical and submicrostructural studies to be a misnomer (cf. brown algae). Although these organism types are linked together in the classification scheme used here, this is tentative as they may be rather unrelated and biochemically distinct.

These organisms have been relatively little studied chemically by comparison with the brown algae. The diatoms and haptophytes secrete hard exoskeletons of aluminosilicates and calcium salts respectively, while the golden algae do not, though they may contain silica microspicules. There are roughly 200 known species of marine golden algae and 500 of haptophytes, but the number of marine diatom species may be as high at 50,000, constituting the bulk of the phytoplankton at certain times of the year, and therefore of crucial importance to marine ecosystems.

The storage polysaccharide of diatoms and Chrysophyceae is **Chrysolaminarin**. Photosynthetic pigments resemble those of the brown algae, with no phycobilins but with chlorophylls c including the more recently discovered **Chlorophyll c₃**. A number of minor xanthophylls have been detected and *Phaeodactylum tricornutum* has yielded some degraded carotenoids such as **Apo-13'-fucoxanthinone**. There have been extensive studies on their lipids on account of their biotechnological importance (cf. algae). The content of sulfur glycerides, especially **1,2-Diacylglycerol 6-sulfoquinovosides** (also found in other classes of organism) is relatively high. The range of known steroids resembles that of the brown algae in being based on limited side-chain modification of the cholestane skeleton, up to C₃₀ in the case of **24-Propylidenecholesterol**, with some sulfation, e.g. **Hymenosulfate**. The **Bacillariolides** appear to be oxylipins produced by the arachidonate pathway. The **Prymnesins** are toxic polyethers produced by a haptophyte.

The range of terpenoids isolated is very narrow and limited so far to simple phytanes. It is noteworthy that in two studied diatom species, the biosynthesis of these (in the chloroplasts) is by a non-mevalonate pathway while the steroids, produced in the cytoplasm, are mevalonate-derived.

Nitrogenous compounds are similarly few in number, but the toxic pyrrolidine **Domoic acid**, also found in red algae, was isolated as a shellfish toxin resulting from *Nitzschia* infection.

Moore, B.S., *Nat. Prod. Rep.*, 2005, **22**, 580–593 (*diatoms*)

3.5 DINOFLAGELLATES (ZH7000)

Note; Many shellfish toxins are now known to be dinoflagellate metabolites but may not currently be classified as such in the database

These monocellular organisms are economically important as the causative agents of toxic 'red tides'. Biochemical and other studies have shown clearly that they are more closely related to the ciliates and to certain other groups than they are to other flagellate organisms. (Kornprobst 2005 describes them as 'Mesocaryotic', i.e. intermediate between the eukaryotes and the Stramenopiles). About 200 species are known, predominately marine. Only just over half are photosynthetic; some are carnivorous. Their main anatomical characteristic is the possession of two flagellae, one equatorial and one longitudinal. Most are unicellular but some are filamentous. They participate in a range of symbiotic associations, especially with corals and with molluscs.

Those organisms which are photosynthetic contain **chlorophylls a** and **c**. They contain a range of xanthophylls, most characteristically the C₃₇ trisnortriterpenoid pigment **Peridinin** and also the structurally unusual **Gyroxanthin**. The characteristic steroids are a range of 4 α -methyl compounds such as **Amphisterol** and **Peridinosterol** representing an intermediate stage between the tetracyclic triterpenoids and the cholestane/ergostane type predominant in the brown algae and relatives. **Gorgosterol**, originally isolated from a gorgonian, was found later to be produced by a dinoflagellate symbiont.

The known toxins of dinoflagellates fall into two main groups, though the exact type of toxin produced is genus-specific. The first main group is polyketide-derived, either long-chain with some cyclic ether formation

(**Amphidinols**, **Luteophanols**, **Colopsinols**, **Zooxanthellatoxins**) or with multiple ether rings ('polyether ladders') (**Brevetoxins**, **Ciguatoxins**, **Yessotoxin** and their analogues, together with the giant C₁₆₄ molecule **Maitotoxin**). Another structural subtype is shown by **Okadaic acid**, while other polyketides are macrolides such as the **Amphidinolides**. The **Prorocentrolides**, **Pinnatoxins** and **Spirolides** are cyclic nitrogenous polyketides which have been isolated from shellfish but are known to be dinoflagellate produced. It is notable that in known cases the biosynthesis of polyketides in dinoflagellates is by a totally different pathway from that in other organisms. The other main class is composed of nitrogenous guanidinoid toxins of which **Saxitoxin** is the prototype.

Moore, B.S., *Nat. Prod. Rep.*, 2005, **22**, 580–593

3.6 FUNGI (ZG)

Fungi are now considered part of the Eukaryote kingdom, and are characterised by the lack of a photosynthetic mechanism and by a mode of life which is saprophytic, parasitic or symbiotic. Another major biochemical difference from algae lies in their cell wall structure usually based on chitin rather than cellulose. Fungi are found throughout a wide range of terrestrial and marine environments and it is not possible to produce a meaningful definition of 'marine fungi', only to refer to a range of halotolerance among the various fungal species that are widely distributed. Thus marine sediments and marine invertebrate tissues yield fungal species from genera also found terrestrially, but which have developed a preference for growing in saline environments. Of the approximately 100,000 fungal species so far described, about 500 have been found in marine environments, but this figure is certain to increase in the light of further research. Many metabolites, such as **Gliotoxin**, have been isolated from both terrestrial and marine fungi, and when the identical compound has not yet been found in a terrestrial fungus, there are often close relatives. One basidiomycete species, *Coriolus consors* (preferred name *Irpex consors*) has been cultivated in both seawater and freshwater and yielded the same natural products. Since fungi are invariably cultivated on a medium which is then extracted, cross-contamination of cultures by terrestrial fungi or bacteria is a possibility that must be guarded against.

The lower fungi or Chytridiomycetes (ZG1000) are found only to a very limited extent. They are taxonomically difficult to classify, resembling the higher fungi in their lack of photosynthesis, but resembling the monocellular algae in having a cellulosic cell wall structure and a flagellate stage, sometimes with alternation of generations. There are different views as to how they should be classified vis-à-vis the simpler Stramenopiles, and several classes of organisms formerly considered to be lower fungi have now been reclassified on biochemical grounds. Chemical studies are limited.

The majority of fungi fall into the category of higher fungi or Eumycetes having typical fungal biochemistry, and which can be subdivided into the four main classes of Zygomycetes (ZG2000), Ascomycetes (ZG3000), Basidiomycetes (ZG4000) and Deuteromycetes (ZG5000). These groups are distinguished by their method of spore formation (zygospores, asci and basidia respectively for the first three groups). The Deuteromycetes are an ill-defined group roughly corresponding with the term fungi imperfecti (the terms Mycelia sterilia and Hyphomycetes are also found according to various schemes). These are fungi in which no reproduction is observable and which are therefore extremely difficult to identify. Spore formation can be induced in some of them under laboratory conditions, work which shows that they are a loose collection of unrelated fungi rather than a true taxonomic group, and can lead to reclassification into one of the other classes. This can lead to taxonomic duplication, with the organism allotted a new name based on the reproductive form (which should take priority) while still retaining its old name.

The Ascomycetes and the Deuteromycetes are the most represented in the marine environment and been the most investigated chemically.

The great majority of fungal secondary metabolites have been isolated from fungi associated with other organisms. Examples of natural products isolated from non-associated marine fungi include the simple polyketide **Phomoxin**, the carotenoid **Neurosporaxanthin** and some indolopeptides from surface waters or marine sediments.

Marine algae (green, red and brown), like higher plants, harbour a wide variety of endophytic fungal species; for example, 116 different fungal strains were cultivated from a single specimen of *Fucus serratus*. It is not in general known whether any particular relationship should be considered as symbiotic, benign or pathogenic. There are usually strong structural similarities between the natural products from these epiphytic marine fungi and their terrestrial equivalents.

Fungal mycelia are also found in marine animal tissues. Evidence for their presence is based entirely on culturing experiments and as yet there is no evidence from direct microscopic examination or other techniques.

Their role is unknown. In general, compounds produced by fungi associated with marine animals are structurally related to other fungal metabolites and are distinct from natural products produced by the animal organisms themselves. It does not appear that fungi are the biogenetic source of natural products isolated from marine invertebrates, unlike the situation found with bacteria. An example of a natural product isolated from a sponge-associated fungus is **Ulocladol**, while **Epicoccamide** is an example of a substance isolated from a fungus associated with a cnidarian (a jellyfish). Other series of characteristic fungal products have been isolated from fungi associated with all other classes of marine invertebrates, as well as from fungi parasitic on fish.

The most characteristic sterols of all fungi are **Ergosterol** and related ergostanes. Reports of 5,7-dienic steroids from other marine species are suggestive of fungal contamination. Other steroids isolated include **Fusidic acid**, and the **Gymnasterones** from an ascomycete-sponge association.

There are very few reports of the incorporation of halogens. Most fungal secondary metabolites are based on a polyketide biogenesis, but some terpenoids are found, for example the unusual nitrobenzoyl esters of **6,7,14-Trihydroxy-8-drimen-12,11-olide** and the **Hirsutanols** from a sponge-associated fungus. The alkaloids obtained from marine fungi are dominated by diketopiperazines/indoles, as is the case with terrestrial fungi.

Very few biosynthetic studies have been reported for natural products specifically from marine fungi.

Dictionary of the Fungi, 9th edn, (eds. Kirk, P.M. *et al*), CABI publishing, 2001

Bugni, T.S. *et al*, *Nat Prod. Rep.*, 2004, **21**, 143–163 (*rev*)

Moore, B.S., *Nat. Prod. Rep.*, 2005, **22**, 580–593 (*rev*)

Ebel, R., *Frontiers in Marine Biotechnology*, (eds. Proksch, P. *et al*), Horizon Bioscience, 2006, 73–143 (*secondary metabolites from marine fungi*)

3.7 PORIFERA (sponges) (ZS)

The sponges are considered as the most primitive of the multicellular organisms, providing an evolutionary bridge between the monocellular eukaryotes and the rest of the animal kingdom. They are multicellular organisms lacking all organ differentiation (including gonads) and some can uniquely reconstitute themselves after passing through a sieve. They are almost exclusively marine. Sponges are found at all marine depths but the proportion of calcareous sponges diminishes with depth owing to the physicochemical effect of pressure on the ability of the organisms to secrete calcium.

The taxonomy of sponges is particularly difficult owing to the paucity of well-marked morphological feature by which they can be distinguished. Many species have been synonymised and genera renamed (e.g. *Aplysina* = *Verongia*), and there are numerous views on their classification at higher levels; a recent multi-volume treatise (Hooper *et al*, 2002) proposes many changes. Three main subdivisions have been generally recognised, depending on the nature of the skeletons that they secrete; calcareous (ZS1000), siliceous or askeletal. The largest group is the demosponges, about 95% of known species, in which the skeleton is of spongine, a proteinaceous polymer similar to keratin. The Hexactinellida sponges, characterised by silica spicules of 6-fold symmetry, are found only at great depth and have been little studied chemically.

In this database a simple classification into four groups is used, which is based on Hooper (2002) as summarised in tabular form by Kornprobst (2005). This divides sponges into; Calcareous sponges (ZS1000), Homoscleromorphous demosponges (e.g. *Plakortis*) (ZS3000), Tetractinomorphous demosponges (e.g. *Stelletta*) (ZS4000) and Ceractinomorphous demosponges, (e.g. *Agelas*) (ZS5000).

Sponges participate in a wide range of symbiotic/commensal relationships, and a large number of the isolations of natural products earlier reported from them are in fact owing to the presence of cyanophytes in particular. It is estimated that the biomass represented globally by sponge-cyanophyte symbionts is greater than that of the sponges themselves. Given the extent of these associations, it is not surprising that the diversity of natural products reported from sponges and sponge aggregates covers the whole range of known types. Other natural products reported may be true metabolites of the symbionts.

A wide variety of cell membrane components have been isolated, not only extensive series of both straight-chain, branched and methylenic (cyclopropanoid) fatty acids but alkylglycerols (e.g. **Raspailynes**) and hopanoids based on **Bacteriohopanetetrol** and relatives as well as a vast range of steroids. There are also numerous brominated and α -hydroxyacids. Certain linear terpenoids such as the **Furospingins** have also been postulated to play a role in membrane structure. Associated with the membrane structure is a wide variety of glycolipids, many of them of unique structural type. The simpler *N*-containing parents are the **Sphingosines**, the Dictionary entries for which include their *N*-acyl derivatives collectively known as ceramides, and their glycosides, known as

glycosphingolipids or cerebroside. More complex types of sphingosine such as the **Plakosides** (containing cyclopropane fatty acids) have individual entries. The nitrogen-free glycolipid content also includes some structural types not found elsewhere, such as the **Crasserides** (ether glycerides of a 5-membered cyclitol), which as a class have been suggested to be uniquely diagnostic of the Porifera and found in all species examined. A unique class of compounds so far discovered only in sponges is the range of carotenoids aromatised in one or both rings such as **Renieratene** and **Tethyanin**.

Among calcareous sponges the most investigated genera are *Clathrina* and *Leucetta*. These genera have yielded in particular long-chain unsaturated aminoalcohols such as the **Leucettamols**, a range of imidazole (e.g. the **Naamines**) and other alkaloids, and cyclic peptides, (e.g. **Leucamide A**).

By far the most studied have been the demosponges, reflecting their numerical preponderance and shallow-water accessibility. Demosponges contain a very wide range of steroids, which encompasses not only the conservatively modified structures biogenetically not far removed from cholesterol (ergostanes, stigmastanes) found in the algae, but also a large number showing more profound modification. These include 19-norsteroids such as **Hapaioside** and a range of A-ring abeoosteroids (3-hydroxymethyl-A-norsteroids). The most common type of modification, however, is further side-chain methylation which leads to an extensive series of steroids having various branching patterns up to C₃₂, (e.g.; C₂₉, **Aplysterol**; C₃₀, **Stelliferasterol**; C₃₁ **Axinyssasterol**; C₃₂ **(26,27-Dimethyl-26-methylenestigmast-7-en-3-ol)**). Side-chain cyclopropasterols such as **Calysterol** and **Aragusterol A** occur in the range C₂₇-C₃₁ and there are also many secosterols with fission at 5,6- (e.g. **Hipposterol**), 8,9- (**Jereisterol A**), 8,14- (**Jereisterol B**) and 9,11- (**Blancasterol**). There are also many polyhydroxylated and sulfated sterols of the type found also in many other marine organisms, and many steroidal glycosides. Halogenated steroids (e.g. **Aragusterol C**) and steroidal alkaloids (e.g. **Plakinamines**) are rare.

Demosponges of the genera *Plakortis* and *Plakinastrella* (order Homosclerophorida) contain a wide range of oxylipins, including many cyclic peroxides such as the **Plakortides**.

Another group of unusual natural products found in sponges are the terpenic isocyanides R-NC such as **7,20-Diisocyanoisocycloamphilectane**, together with their related isothiocyanates R-NCS, isocyanates R-NCO and formamides R-NHCHO. In the appropriate DMNP entries these are grouped as derivatives under the parent isocyanide, reflecting the fact that they have a common biogenetic origin, the isothiocyanates and formamides apparently being derived *in vivo* from the isocyanides (and not the other way round as was formerly proposed). However the biogenetic origin of the isocyanides themselves has not yet been completely solved.

A wide range of alkaloids and terpenoids are found in demosponges. Indole alkaloids range from simple halogenated indoles such as the **Plakohypaphorines** to polycyclics such as the pentacyclic pyridoacridines (e.g. **Meridine**). Demosponges are the most prolific of all marine organisms in terms of the secondary metabolites that have been isolated from (but not necessarily produced by) them. In order to get a good overview, the best route is to search the CD-ROM version of the Dictionary using the search term **ZS*** (all sponges), but further information can also be obtained from the introductory sections dealing with terpenoid and alkaloid types, and of course by perusing the pages of the printed Dictionary.

Faulkner, D.J. *et al*, *Pure Appl. Chem.*, 1994, **66**, 1983–1990 (rev)

Fattorusso, E. *et al*, *Progress in the Chemistry of Organic Natural Products*, (eds. Herz, W. *et al*), SpringerWien, New York, 1997, **Vol. 72**, 215–301 (rev, *sponge glycolipids*)

Watanabe, Y. *et al*, *Sponge Sciences: Multidisciplinary Perspectives*, Springer, Tokyo, 1997 (*book*)

Kuniyoshi, M. *et al*, *Recent Advances in Marine Biotechnology*, (eds. Fingerman, N. *et al*), Science Publishers, USA, 2001, **Vol. 6**, 29–84 (rev)

Systema Porifera: A Guide to the Classification of Sponges, (eds. Hooper, J.N.A. *et al*), Kluwer/Plenum, New York, 2002 (*book*)

Moore, B.S., *Nat. Prod. Rep.*, 2005, **22**, 580–593; 2006, **23**, 615–629 (rev, *biosynth*)

3.8 CNIDARIA (medusae, sea anemones, hydroids and corals) (ZT)

This class of organisms represents the first major development in body-plan over the undifferentiated sponges, showing cellular differentiation into cells with different functions, but in general no well-defined organs. The term Cnidarian replaces the older ‘Coelenterate’. This is a class of organisms typified by a carnivorous lifestyle, the presence of specialised stinging cells (cnidocytes) used in the capture of prey and defensively, and a digestive system consisting of a sac with only one opening. They have a basically radial body plan, which may be modified either in the direction of a fixed polyp with a central gastric cavity (hydras), or a free-swimming medusa form (jellyfish) in which the gastric cavity is underneath. Reproduction is sexual, producing a free-swimming larval

planula which develops into a free-swimming followed by a polyp form, although in some species only one of these is formed.

About 10,000 species are documented, classified into two subphyla. The first subphylum (Anthozoa) comprises the sea-anemones, gorgonians, crinoids and corals which have no free-floating phase, and a skeletal structure consisting either of secreted calcareous minerals, or of proteinaceous material (gorgonine, analogous to the spongine found in the sponges). The anthozoa are divided into two groups depending on their symmetry; eightfold in the octocorals, (alcyonians or soft corals and gorgonians) (ZT1000) or sixfold or a multiple of sixfold (hexacorals, including the sea anemones and hard corals) (ZT2000). The former subphylum is the most studied group of the cnidarians chemically.

In general, relatively few nitrogenous secondary metabolites have been isolated. The proportion of halogenated metabolites is also relatively low, except for halogenated briaranes from *Briareum* spp., such as the **Briareins**. Some sea anemones owe their colour to carotenoids including **Peridinin** and **Actinoerythrin**. The former in particular is produced by dinoflagellates, and these carotenoids work their way up the food chain to molluscs. Octocorals are rich in prostanoids, steroids, terpenoids (but only sesqui- and diterpenes) and aromatics. The prostanoids include a number identical with those found in higher organisms of the **Prostaglandin** series (A, B, E and F), but also halogenated prostanoids containing Cl, Br and I such as the **Chlorovulones**, especially from *Clavularia*. Further oxylipins are now being found in other cnidarians and it appears that their presence may be ubiquitous. Series of furanoid compounds similar to **Ancepsenolide** elsewhere in the phylum support this hypothesis. The hexacorals contain a range of polyunsaturated long-chain acids such as **Leiopathic acid** and the **Montiporynes**.

Like the sponges, cnidarians contain a wide range of sterols, both typical cholesterol-related, and those with modified side-chains. An important class is the side-chain cyclopropanoid steroids based around **Gorgosterol**, although it has been shown that these are in fact produced by symbiotic dinoflagellates. **Yonarasterol I** is an example of this group showing halogenation at C-6. There are many polyhydroxylated steroids, often showing side-chain epoxidation, for example the **Hippuristerols**, and a considerable number of secosteroids, some of unusual type such as **Nicobarsterol**. Also are encountered pregnane glycosides (**Verrucoside**, **Pregnediosides** and others). In contrast to the sponges, however, *O*-sulfation is absent. The hexacorals produce polyhydroxylated ecdysteroids such as **Zoanthusterone** which are thought to protect the organism against crustacean larvae.

The sesqui- and diterpenes found in the octocorals are diverse and include some skeletons unique to them (nardosinanes, capnellanes, sterpuranes and some others), which in most cases are unique to certain families. In contrast, terpenoids are almost absent from the hexacorals. The sesquiterpene hydrocarbon content of octocoral tissues may be exceptionally high and they are thought to play an ecological role as predator and larval implantation repellents. An important feature is the frequent occurrence of common terpenoids of the enantiomeric series to that familiar from terrestrial plants, as shown for example by **γ -Maaliene** and **α -Copaene**. There is a complete absence of the isocyanides characteristic of the sponges, and only a limited range of terpenoid alkaloids such as **Clavulinin**. The well-known skeletons represented include many furanoterpenes. The hexacorals have yielded only a few sesquiterpenes; some lepidozanes and secolepidozanes, e.g. **Anthoplalone**.

The octocorals are very rich in diterpenoids, with over 1500 belonging to 50 skeletal types isolated. As with the sesquiterpenes, some skeletons are widespread throughout the phylum, while others are restricted to a single family and can be considered as chemotaxonomic markers. Particularly widespread skeletons include cembrane (including norcembranes and some dimers such as **Sinuflexlin**), xenicanes, lobanes, briaranes, cladiellanes, dolabellanes and amphilectanes. As with the sponges, many skeletons are prenylogues of widespread sesquiterpenoid skeletons. The briaranes are particularly numerous and unlike most other skeletons, frequently halogenated (chlorine only).

Some diterpene alkaloids have been found such as the **Sarcodictyins** (imidazoles containing the eunicellane skeleton, closely related to briarane). The hexacorals produce a range of ceramides, often containing unusual sphingosines, and some other acyclic amides such as **Sinulamide**. Their range of cyclic alkaloids is restricted, e.g. the **Villagorgins**, **Calliactine**, but includes the unique class of fluorescent pigments based on the cycloheptadiimidazole skeletons of **Parazoanthoxanthin A** and **Pseudozoanthoxanthin A**.

Hexacorals of the order Zoantharia (genus *Zoanthus*) have yielded a range of polyketide alkaloids similar to **Zooxanthellamine**. Chemically and pharmacologically, the most significant natural product isolated from cnidarians is probably **Palytoxin**. Hexacorals inhabiting surface waters also contain a range of mycosporins such as **Mycosporin-Gly** which are closely related to analogues found in fungi and appear to perform a photoprotective function. They also contain a range of small nitrogenous betaines and other amines, some purines such as **Caissarone**, and some simple indole-imidazole alkaloids centred on **Aplysinopsin**.

The other subphylum of cnidarians (Medusozoa) comprises the Cubozoa (box jellies, ZT5000), Hydrozoa (hydras, ZT6000) and Scyphozoa (true jellyfish, ZT7000). Chemical studies have been mostly confined to their venoms, which are peptides. (See for example the entry for *Anemonia sulcata* **Toxin**). One difficulty associated with studying their secondary metabolites is the large amount of water in the tissues, which can reach 98%. Some steroids have been identified, plus a small range of polyketides e.g. **Solandelactones**, **Lytophilipines**, and some anthracenoids, e.g. **Garvins**, and simple alkaloids, e.g. **Corydendramines**, **Tridentatols**. There are also the nitrogenous compounds associated with the bioluminescence of some species; *Cypridina* **Luciferin** and **Coelenterazine**.

Faith, F.M.Y. *et al*, *Recent Advances in Marine Biotechnology*, (eds. Fingerhahn, N. *et al*), Science Publishers, USA, 2001, **Vol. 6**, 85–100; Venkateswarlu, Y., *ibid*, 101–143 (revs, coral)
Anderluh, G. *et al*, *Toxicon*, 2002, **40**, 111–124 (rev, anemone toxins)

3.9 PLATYHELMINTHES (flukes, tapeworms and free-living flatworms) (ZU1000)

These are the flatworms, characterised by a bilateral body plan and the complete absence of a digestive cavity. About 18,000 species are known. They may be terrestrial, freshwater or marine and many belong to orders which are exclusively parasitic (e.g. flukes). The majority of marine species belong to the class of planarians (turbellarians). These are mobile, carnivorous animals having no physical means of defence and relying entirely on substances absorbed or modified from the diet, or produced by symbiotic organisms, as chemical antifeedants. The most studied genus is *Amphicolops*. These worms are protected by **Amphidinolides** produced by symbiotic dinoflagellates and contain other dinoflagellate products such as **Luteophanols**. Other planarians feeding on ascidians have yielded alkaloids (e.g. **Lepadins**, **Villatamines**).

3.10 ANNELIDA (trueworms) (ZU3000)

These are the segmented worms, having an alimentary canal. They include the polychaetes, oligochaetes (earthworms; mostly terrestrial), hirudineans (leeches; mostly freshwater), echiurians and Vestimentifera. They locomote by means of bristles which can be irritant or venomous. The best-known genus among the echiurians is the spoonworm *Bonellia viridis*, most studied on account of its tetrapyrrole pigment **Bonellin** which also plays a role in inducing sexual differentiation in the larva. The Vestimentifera include the recently-discovered giant hydrothermal vent dwellers *Riftia* which coexist with sulfur bacteria, and store elemental sulfur in the tissues.

There has so far been little study of lipid or steroid content. Their carotenoid pigments appear to be mainstream components such as **Astaxanthin**, derived dietetically. Other annelid pigments are anthracenes and anthraquinones, such as **Hallachrome**. Annelids also contain brominated phenols (e.g. **2,6-Dibromophenol**) and derived aromatics such as **Thelepin**, which protect them against bacteria.

Certain annelids bioluminesce and in *Odontosyllis* spp. this is based on pteridines such as **6-Propionyllumazine**. **Nereistoxin** is a simple aminodithiolane with powerful cytotoxic properties produced by *Lumbriconereis* sp. Some annelids contain large amounts of **Hypotaourine** and **Thiotaourine**.

3.11 OTHER VERMIFORM GROUPS (ZU5000)

The ribbon-worms or nemerteans have yielded the powerful nicotinic receptor agonist **Anabaseine**, used as a venom by the worm, together with several related oligopyridines. Toxins of the tetrodotoxin series are also found in the tissues, and also some peptide toxins, which have only been investigated fully for one species, *Cerebratulus lacteus* (see **Neurotoxin B-IV**)

The unsegmented phoronidian worms *Phoronopsis* have yielded antibacterial bromophenols like those obtained from the annelids.

3.12 BRYOZOA (ZU6000)

These colonial organisms are entirely aquatic and mostly marine. They are distinguished by their unique form of gastric cavity, which is surrounded by tentacles forming an organ called the lophophore. The colonies are produced by budding and therefore consist of genetically identical individuals, each of which is surrounded by a bilayered exoskeleton, the inner layer calcareous (not always continuous) and the outer layer chitinous. They are suspension feeders, feeding on plankton and bacteria, and are found at all depths.

Bryozoans have so far been less studied than the number of known species (5700) would justify given the range of interesting natural products already isolated from them. This is probably a consequence of the difficulty of harvesting them.

Terpenoids and steroids have been little studied. A number of common mono-, di- and triterpenes (e.g. Cuminol, Neoabietic acid, Ursolic acid or a stereoisomer) were reported from *Conopeum* sp., but this work needs confirmation. The single diterpenoid **Murrayanolide** that has been obtained apart from this work has a unique skeleton which implies that many more unusual terpenoids may exist on other bryozoans. The similarly limited studies of steroid content have yielded only relatively common types based on cholestane methylated in the side chain and/or hydroxylated. One or two anthraquinone pigments have been characterised, of which the most unusual is **Bryoanthrathiophene**.

The most numerous metabolites from bryozoans are defence chemicals, which comprise numerous alkaloids, and the **Bryostatins**, an important series of polyether polyketide toxins with anticancer properties, some of which have also been found in other marine organisms. The ultimate source of these may be *Candidatus* bacteria.

The range of alkaloids is extensive taking into account the limited amount of work that has so far been done. There are simple halogenated phenethylamines (**Convolutamines**, **Volutamides**). Pyrroles and pyrrolidines include **Tambjamines** (originally isolated from animals higher up the food chain, and which could be tetrapyrrole degradation products), **Amathamides**, **Amathaspiramides** and **Convolutamides**. Indoles are mostly brominated simple indoles (**Flusrabromine**, **Alternatamides**) but *Flustra foliacea* yielded a series of **Flustramines** and related alkaloids of the physostigmine type (VX4100) unique in the marine environment. The **Securamines**, **Chartellines** and **Chartellamides** represent a further elaboration of this structural type up to a maximum of seven rings. There are also a number of quinolinequinones, halogenated or bearing thioether substituents (**Perfragilins**, **Caulibugulones**). The presence of nitro groups in a few alkaloids including the purinoid **Phidolopin** is notable.

Kerr, R.G. *et al*, *Recent Advances in Marine Biotechnology*, (eds. Fingerman, N. *et al*), Science Publishers, USA, 2001, Vol. 6, 149–164; Prinsep, M.R., *ibid*, 165–186; Kem, W.R., *ibid*, 187 (*revs*)

3.13 MOLLUSCA (ZV)

This is a diverse and widely distributed phylum of organisms. The body plan is basically nonsegmented and bilateral, although in some molluscs (the gastropods) it is often modified by torsion into a spiral surrounded by a shell. There are well-developed organs inside a more or less thickened outer layer, the mantle, which secretes a shell formed of calcareous matter and protein. This shell may be external, as in the gastropods, internal as in squids, or may be totally lacking (octopuses and nudibranchs). There is generally a muscular foot and a cephalic region which may be highly developed into tentacles and other organs, as in the cephalopods. The alimentary canal is well developed and furnished with a rasping radula used in feeding. Different classes of molluscs show variation in this general body plan, for example the bivalves have a hinged shell, no cephalic region and no radula, and some of them also lack the foot. Many species of mollusc are known, present in marine, freshwater and terrestrial environments, ranging in size from microscopic to very large. They show a wide range of dietary behaviour (carnivores, herbivores, filter feeders and detritus feeders) and undergo a wide range of symbiotic relationship. In particular, in some molluscs the mantle incorporates symbiotic algae providing toxic antipredator substances.

The phylum is usually divided taxonomically into seven unequal classes, but of these four (including Chitons, ZV1000) are numerically limited and have been studied chemically little or not at all. The most important classes both in terms of number of species, economic importance and chemical studies are the gastropods (ZV2000, ZV3000, ZV4000), the bivalves (ZV6000) and the cephalopods (ZV8000). However, the bivalves with their well-developed physical protective mechanism of the double shell, appear to have less need for chemical defence mechanisms and their secondary metabolites are less profuse. They have mostly been studied in terms of their economically important shellfish toxins, which are in fact microbial/dinoflagellates products. The cephalopods too have been rather little studied; their most characteristic metabolites are **Adenochromines**. The most studied organisms chemically have been various types of gastropod which have little or no physical defence and rely almost entirely on chemical defence against predators.

The numerous gastropods are sometimes further divided into three subclasses, the Prosobranchia (ZV2000) the Opisthobranchia (ZV3000) and the Pulmonata (ZV4000). (This division is not recognised by the Catalogue of Life, but since it is a convenient subdivision of a large group of natural product-producing organisms it is followed here). A table of these subdivisions is given in Kornprobst (2005), Chapter 23, which also gives a more detailed description of the secondary metabolites of gastropods organised by class and subclass.

Terpenoids are numerous. The genus *Planaxis* (Gastropoda, Prosobranchia) has provided a series of cembranoids such as **Jeunicin** and **Planaxool**. Among the opisthobranchs, the sea hares or aplysians, which are herbivorous, feed on cyanobacteria and algae, and their digestive systems and mantles contain a wide variety of unchanged and metabolised secondary metabolites which perform an antifeedant function. These alimentary chains are complex and have been much studied. The two most studied genera are *Aplysia* and *Dolabella*; the former feed mostly on red algae and contain many halogenated and nonhalogenated terpenoids (**Kurodainol**, **Aplysin 20**, **Brasilanol**, **Punctatol** and many others), cyclic halogenated ethers (**Dactylone**, **Aplyparvunin**, etc.), lactones (e.g. **Aplylides**, **Aplyronines**), and both peptide and nonpeptidal alkaloids (**Aplaminone**). *Dolabella* spp. feed on brown algae, and in accordance with the terpenoid profile shown by these, contain mostly nonhalogenated diterpenoids (**Auriculol**, **Dolatriol**) as well as lactones (**Dolabelides**), peptides (notably the extensive range of highly cytotoxic **Dolastatins**, from cyanobacterial symbiosis) and alkaloids. A few *Aplysia* spp. feed on brown algae and also contain nonhalogenated diterpenes, e.g. **4-Hydroxycrenulide**. Other products isolated from this type of mollusc appear to derive from symbiotic/commensal green algae (**Aplylides**) and even fungi (**Aplysiatoxin**).

The shell-less nudibranchs can incorporate cnidocysts obtained from cnidarians into their mantle, and also rely heavily on compounds, especially terpenes, ingested in the diet as a means of defence. A wide range of skeletal types have been isolated, and include sponge-derived terpenoid isocyanides and compounds derived metabolically from them, such as the **Acanthenes**, and sponge-derived scalarane sesterterpenoids such as **Deoxoscalarin**. However, nudibranchs also synthesise terpenoids *de novo* via the mevalonate pathway. Many terpenoids are present as glyceryl esters such as the **Anisodorins** and the **Verrucosins**. In general it is possible to predict with a fair degree of accuracy what types of compound (though not necessarily the exact compounds) that will be isolable from nudibranch tissues by studying the prey of the different species. The sacoglossan gastropods also contain a range of terpenoids, but these animals are herbivorous and the terpenoids derive from commensal green algae entering into the tissues (e.g. **Ascobullins**). A number of degraded chlorophylls such as **Chlorophyllone a** have been isolated from bivalve molluscs, which have also yielded modified carotenoids (**Pectenoxanthin**, **Crassostreaxanthins**).

Nudibranchs contain a narrow range of carotenoids (e.g. **Hopkinsiaxanthin**) and steroids (**Lovenone**, a secosteroid, for example). Other defence allomones include quinonoid and related meroterpenoids, and macrocyclic lactones (**Laulimalide**, **Sphinxolides**, the isoxazolidone lactone **Kabiramides** and others, some of these at least probably cyanobacterially derived). Also noteworthy is the isolation of prostanoid lactones from *Tethys fimbria*.

The distribution of polyketides in molluscs is patchy. They are found only in some classes of the gastropods, for example the **Auripyrones** (strictly, polypropionates) from *Dolabella*, the **Aglajnes** from *Bulla* spp. which are preyed upon by carnivorous molluscs *Aglaja*, and **Tridachiapyrones** from the herbivorous sacoglossans. Pulmonarians have afforded a number such as **Muamvatin**, **Maurapyrone C** and the **Onchitriols**.

Long chain aromatic and heteroaromatic metabolites, which do not appear to be derived from the diet, are found in *Navanax* spp. (**Navenones**, which play a role as alarm pheromones), *Haminoea* spp. (**Haminols**) and other genera.

Peptides, especially cyclic oligopeptides often containing unusual amino acid residues, are probably widely distributed and show structural resemblances to similar compounds found further down the food chain, e.g. in sponges. See for example the **Kulolides** from *Philinopsis* spp. Peptides such as the **Kahalalides** have also been isolated from sacoglossans, and **Onchidin** is an example of a cyclic oligopeptide isolated from a pulmonarian. Nudibranchs also contain some characteristic nucleosides such as **Doridosine**.

Among other nitrogenous metabolites, the best-known from gastropods is the dyestuff **6,6'-Dibromoindigotin**, known since ancient times. The genus *Lamellaria* (Gastropoda; Prosobranchia) yielded a wide range of the pyrrole alkaloids. The **Lamellarins**, which, however, are also found in ascidians on which the molluscs feed and in sponges, are probably biosynthesised symbiotically. Other gastropods (nudibranchs) prey on bryozoans, and yield the **Tambjamines**, which are also pyrroles. There are also guanidine alkaloids, e.g. **Triophamine**.

Similarly, the **Kuanoniamines** from *Chelynotus* (Gastropoda; Mesogastropoda) are closely similar to, though not identical with, **Dercitine** and similar alkaloids isolated from sponges. Other compounds isolated bearing a close structural relationship to sponge products include **Jorumycin**, which closely resembles the **Renieramycins** from sponges.

Carnivorous gastropods of the genus *Conus* produce a vast series (there appear to be tens of thousands of chemically distinct compounds) of highly toxic peptides the **Conotoxins**, which are delivered to the prey by means of a highly specialised injecting organ. Other toxic molluscs lack this specialised delivery system and administer

toxins through the radula. Such toxins are complex alkaloids related to **Tetrodotoxin** and **Surugatoxin** and are bacterial products (see also under fish, below).

The bivalve toxins (**Yessotoxins**, **Pectenotoxins**, **Pinnatoxins**, **Azaspiracids**, **Saxitoxins**) responsible for various kinds of shellfish poisoning are mostly produced by commensal dinoflagellates and have been mentioned above. There are differences in the distribution of different members of the saxitoxin series between the tissues of the bivalves and the originating dinoflagellates.

The kidneys of the giant clam *Tridacna maxima* concentrate up to 0.1% of arsenic, the function of which is unknown. It is stored as various dimethylarsinoylribosides.

Cimino, G. *et al*, *Curr. Org. Chem.*, 1999, **3**, 327–372 (rev, *opisthobranchs*)

Molluscs: From Chemico-ecological Study to Biotechnological Application; Progress in Molecular and Submolecular Biology, (eds. Cimino, G. *et al*), Springer, 2006, **Vol. 43** (book)

3.14 ECHINODERMATA (ZW)

These organisms are characterised by a radially symmetrical body plan, (which is acquired in the adult stage, the larvae being bilaterally symmetrical) and a unique system of respiration through water-filled tube feet which also provide locomotion. There is a calcareous endoskeleton. This is the largest phylum of exclusively marine animals, with about 7000 species known. They may be herbivores, suspensivores, detritivores, carnivores or necrophages, and the carnivorous species may prey for example on corals or other echinoderms. There are many examples of commensalism and parasitism between echinoderms and other organisms.

Although various classification schemes for echinoderms differ in detail, five main groups are generally recognised. The taxonomy used in this Dictionary follows the Catalogue of Life scheme. The most primitive, widely represented in the fossil record, are the Crinoids (ZW1000) in which the mouth and anus are on the same surface. They have a planktonic larval form followed by an adult form which may be sessile (sea lilies) or mobile (feather stars). The other four groups, in which the mouth and anus are on opposing faces, are the starfish (Asteroidea) (ZW2000), sea urchins (Echinoidea) (ZW3000), sea cucumbers (Holothuroidea) (ZW4000) and brittle stars (Ophiurioidea) (ZW5000).

The presence of steroidal saponins of different types in the starfish and in the sea urchins is unique in the animal kingdom, and serves to delineate them from the other echinoderms and from each other. Other characteristic markers are the dominance of 3 α -hydroxylated steroids in the ophiurians, and of quinonoid pigments of different types in the crinoids and in the sea urchins.

The various types of echinoderm produce a variety of specialised polysaccharides, the study of which is still in its infancy. One which has been characterised is **Frondecaside**. The lipid content of sea urchins and ophiurians is high in polyunsaturates. The starfish have been relatively little investigated but appear to follow the same pattern, with some prostanoid precursors. A high proportion of branched-chain acids have been isolated from sea cucumbers, but these are probably of bacterial origin. Phospholipids and glycosphingolipids appear to be universally present in echinoderms and a wide range of structural types of ceramides and cerebrosides have been isolated from starfish (see **Acanthacerebrosides**, **Astrocerebrosides** and similar compounds) and holothuroids. About 30 different carotenoids have been characterised from sea urchins, mostly from the gonads, including the apocarotenoid **Paracentrone**, and others from ophiuroids (**Ophioxanthin**). The starfish are pigmented by carotenoids derived from the food chain and often modified by the introduction of oxo functions to give pigments of bluer colour, such as **Adonixanthin**.

Throughout the echinoderms, halogenation is rare and found only in a few anthraquinone pigments such as the **Gymnochromes** (from crinoids). There are also few alkaloids of greater complexity than a range of aliphatic amines. The few exceptions to this generalisation are very probably derived from organisms such as dinoflagellates present in the food chain. **Asterina 330** is a mycosporin analogue related to such compounds found in cnidarians. The identification of some unusual sulfur compounds is also noteworthy, for example the **Hedathiosulfonic acids**.

As noted above, the type and extent of steroid content is a major distinguishing feature of different types of echinoderm. The crinoids and echinoids have been little studied, but appear to contain exclusively 'classical' steroid types closely related structurally to cholesterol. The ophiurians, which in some respects are intermediate between the primitive crinoids and the more highly evolved echinoderms, contain many 3 α -hydroxysteroids with only one or two glycosides. In the starfish, the range of glycosides and of steroid sulfates is extensive, derived from a wide range of side-chain modified parent steroids, which, however, are mostly 3 β -hydroxylated. The side chain may be degraded (e.g. **Asterosterol**, **Hermaphrodiol**) or cyclopropanated (**Acanthasterol**). Polyhydroxylation/

O-sulfation of the steroid nucleus, which is widespread in marine organisms, is at its most extensive here. The glycosides, such as the **Asterosaponins** play a role in chemical defence through their surface-active properties. Both pentose and hexose residues are found.

The holothurians contain many steroids, some biosynthesised *de novo* from acetate via lanostane triterpenes, others apparently derived from the diet. In *Holothuria*, it has been shown that two biosynthetic routes operate, one via **Lanosterol** and the other via **Parkeol**. These biosynthetic routes provide steroids with all combinations of presence or absence of the methyl groups at C-4 and C-14, as well as side chain variations (cholestane, ergostane and further additional carbons). The chief distinguishing feature of the holothurians, however, is the exclusive occurrence of specialised triterpenoid glycosides of the holostane type, the prototype for which is **Holothurinogenin** but with well over 100 currently known. These appear to be derived biogenetically via Parkeol. A smaller group showing (19→16) lactonisation is based on **Posietogenin**.

Examples of the anthraquinonoid pigments that are readily extracted from crinoids include **Ptilometric acid**. Some of these are O-sulfates, e.g. **Comantherin sulfate**. The sea urchin pigments however are exclusively naphthoquinonoid, e.g. the **Spinochromes**. The number of alkaloid-like compounds isolated from echinoderms is extremely limited, e.g. **Asterina 330** (a palytoxin analogue).

Stonik, V.A. *et al*, *J. Nat. Toxins*, 1999, **8**, 235-238 (rev. *holothuroid toxins*)

Moore, B.S., *Nat. Prod. Rep.*, 2006, **23**, 615-629

3.15 CRUSTACEA (ZX8000)

The crustaceans, including the decapods, are the only type of animals in the vast arthropod phylum (ZX) that occur to any extent in the sea. (There is also the horseshoe crab *Limulus*, an ancient animal related to the arachnids, and which has a few mentions in this Dictionary, and a few saline-tolerant millipedes living in shore environments). In the past the crustaceans have been considered a separate phylum, but they are now often considered a major subphylum of the arthropods having in common the hard chitinous exoskeleton and the body divided into head, thorax and abdomen. About 60,000 species are known, some of them (ostracods, e.g. *Cypridina*, and copepods, e.g. *Calanus*) very small planktonic organisms. The best-known large species are the decapods (crabs and lobsters). **Chitin**, derived industrially from crab shells, is an important industrial material.

Chemical studies on crustaceans have been fragmentary and are mostly confined to their carotenoid pigments, some of which have also been obtained from other marine organisms but which were originally characterised as crustacean products. These are mostly derived by a variety of oxygenations of the terminal rings of the carotenes, and include **Astaxanthin**, **Crustaxanthin**, **Zeaxanthin** and various others.

The moulting hormones of crustaceans are terpenoid (**Methylfarnesate**) and steroidal (**Ecdysone/Crustecdysone**), the latter being common to insects also. Steroid studies have been fragmentary and have indicated a preponderance of cholesterol and closely related compounds. Various endohormones such as testosterone, similar to their mammalian equivalents, have been shown to be present in crustaceans but these are mostly not included in the Dictionary.

The simple pyridine **Homarine** and the arsenical **Arsenobetaine** are widespread in nature but were first isolated from crustaceans.

3.16 HEMICHORDATA (ZY1000)

This is a numerically limited class of animal (about 100 species recorded), consisting of two surviving types of organism; the acorn worms (Enteropneusts) inhabiting temperate and tropical waters, and the pterobranchs, colonial animals inhabiting chitinous tube galleries and found in polar waters. There is differentiation of the body into three well-defined zones, and they have some but not all of the morphological characters that define the chordates. Two types of natural product have been identified from them. The first is a range of toxic cyclohexanes (e.g. **Bromoxone**), halogenated phenols (e.g. **2,4-Dibromophenol**) and halogenated indoles (**Glossobalol**) isolated from *Ptychodera*, *Balanoglossus* and *Glossobalanus* spp. respectively. These are used by the worms as defence chemicals, and are of environmental significance. Of greater biochemical interest are the highly cytotoxic disteroidal metabolites the **Cephalostatins** from *Cephalodiscus gilchristi*. Owing to the difficulty of culturing hemichordate species, there is no information currently available concerning their possible distribution elsewhere in the phylum, or on their biosynthesis.

3.17 PROTOCHORDATA (ZY5000)

These simplest chordate animals are generally divided into two unequal groups; the urochordates (tunicates) and the cephalochordates which are free-swimming bilaterally symmetrical animals (*Amphioxus*). Protochordates are the most developed of the invertebrates and have a notochord which is the evolutionary precursor of the spinal column characteristic of the vertebrates. They are exclusively marine. The larger group of urochordates is divided into three classes. Of these, two, including the free-floating salps, have been little investigated.

Most chemical studies have been on the third group, the sessile ascidians or sea squirts. These are filter feeders, often harbouring commensal cyanobacteria and other organisms which may be the true source of some of the reported natural products. Their chemistry is dominated by the presence of an extraordinary range of mostly biologically potent nitrogen compounds. The ascidians also famously accumulate vanadium to a very high concentration in specialised cells, and some have highly acidic tissues (down to pH 1). Other metals are also accumulated, as shown by the presence of **Tunichlorin**, probably the product of metabolism of a commensal organism.

The epidermis of ascidians contains a range of sulfated glycans, including some unusual residues such as L-Iduronic acid, and the unusual polysulfated polymannose **Kakelokelose**. The membrane lipids have been little studied, and presumably are close to those of other higher organisms in structure. A few oxylipins have been isolated, such as **Didemnilactone** and **Lissoclinolide**. Ceramides and cerebrosides appear to be widespread as in the echinoderms, with some unusual types such as **Didemniserinolipids** isolated. Ascidians contain a range of carotenoids, both common ones and some rarer ones such as **Halocynthiaxanthin** and **Amarouciaxanthins** probably derived from metabolic alteration of commoner carotenoids present in the filtered plankton. The steroids so far identified lack the wide structural range shown by the echinoderms and are mostly straightforward cholestanes and ergostanes, with some 5,8-epidioxysteroids and secosteroids, e.g. **Aplidiasterols**. The **Ritterazines** from *Ritterella* have disteroid structures linked by a central pyrazine ring, showing close structural similarity to the cephalostatins from hemichordates.

Non-nitrogenous secondary metabolites are few in number. These include some small acetogenins such as the **Didemnenones**. Terpenoids are rare; the **Haterumaimides** are unusual not only in being diterpenes but also in being chlorinated; however, they may derive from *Prochloron* symbionts. *Ritterella* spp. provided some furanoterpenoids related to Dendrolasin such as **8-Hydroxydendrolasin** but Dendrolasin itself was not present, and the depth of dredging would rule out a sponge symbionts, so their origin is obscure. Several series of meroterpenoids have been isolated, especially from the Polyclinidae, such as the **Verapliquinones** and the structurally complex ansa-compounds the **Longithorones** from *Aplidium*.

Among the nitrogenous metabolites, many of which doubtless also spring from commensal organisms, there is a very wide range of structure including some with, and some without, analogies in other phyla.

Firstly, there is an extensive range of modified peptides and depsipeptides. Several series of these are macrocyclic thiazoles and oxazoles, for example the **Comoramides**, the **Bistratamides**, the **Lissoclinamides** and the **Patellamides**. Other cyclic depsipeptides are more strictly peptide-related, although containing a range of unusual amino acids. The most studied have been the **Didemnins** and their relatives.

Heterocyclic alkaloids are numerous and include the extensive range of pyrroloisoquinolines the **Lamellarins** which were first isolated from molluscs but which are the products of ascidians on which they prey, or possibly of a symbiotic association involving sponges. These, like the **Ningalins**, are probably derived biosynthetically from **DOPA**. Quinoline alkaloids are represented by the **Trididemnic acids** and the basic quinoline ring system is further elaborated into pyridoacridines, e.g. **Ascididemin** and other polycycles. These too are also found in other marine organism classes. In the ascidians they fulfil the role of pigmentation, and are also mostly cytotoxic.

Indole alkaloids are also numerous, again known mostly as polycyclic condensed systems, e.g. **Fascaplysin**. For a fuller count of the numerous ascidian alkaloids, it is necessary to search the main body of the Dictionary. Ascidians also contain a wide range of sulfur compounds, both sulfur-heterocycles and polysulfides, such as the aromatic **Lissoclinotoxins**.

Davidson, B.S., *Chem. Rev.*, 1993, **93**, 1771–1791 (rev)

3.18 PISCES (fish) (ZZ1000)

The fish represent the most numerous of marine vertebrates. They are well studied taxonomically and extensively documented in the online database *Fishbase* (a contributor database to the Catalogue of Life). They can be divided into cartilaginous fishes (e.g. sharks), and the larger category of bony fishes, considered to be the more highly evolved. Their commercially important lipids have been extensively studied; see for example **Squalene**.

The cartilaginous fishes contain a wide range of polyhydroxylated nitrogenous and non-nitrogenous sterols, based on 5 β -cholestane. Examples are **Chimaerol** and the important drug **Squalamine**. The colour of different fish is due to the presence of various carotenoids and xanthophylls, including **Astaxanthin**, **Salmoanthin**, **Idoxanthin** and **Tunaxanthins**.

The sexual development of many species of fish is determined by the presence of steroids in the water. Many of the studies have been on freshwater species such as the goldfish, but 17 α ,20 β -Dihydroxypregn-4-en-3-one as its 20-sulfate is known to be a hormone of the male Atlantic salmon together with Testosterone.

The fish products that have received the most chemical attention, apart from the lipids, are the toxins produced by various species. These may be steroidal (e.g. **Pavoninins**), peptide (**Grammistins**) or alkaloid-like, such as the much-studied **Tetrodotoxin** and its relatives from fugu fish (various species of the Tetraodontidae). The latter, however, are metabolites of *Pseudomonas* bacteria or dinoflagellates in the fish, and are also found in other marine organisms and even terrestrial ones.

Some fish secrete peptide venoms in specialised spines to deter prey. An example is the powerful poison **Stonustoxin** from the stonefish.

