Chapter 9

Concluding Thoughts on the Future of Marine Biotechnology

The world's oceans cover more than 70% of the earth, but knowledge of this significant component of the environment is relatively incomplete, compared to that available for the terrestrial sphere. Water, vital for life on the planet, drives many important processes, both geological and biological. The oceans, for example, moderate climate, and store CO₂. The oceans also are important sources of food, minerals, and natural products. Unfortunately, it is often assumed that the oceans have an unlimited capacity to absorb the wastes of civilization, an assumption proving faulty as data are gathered on the extent and effects of pollution, especially on the world fisheries. In view of the need for information on the marine environment, it is not surprising that the age of biotechnology, which began in the early 1970s and, now, twenty years later, has reached revolutionary proportions, stems from experiments done with terrestrial microorganisms, plants and animals, leaving the marine aspects of biotechnology unexplored and under-exploited.

Reflecting the diversity of science, marine microbiologists applied some molecular genetics to the research in the early 1970s, but marine biologists in the early 1980s began to apply the methods of molecular biology more extensively. By the late 1980s, interest in biotechnology applied to marine organisms reached a critical level, measured by the number of publications in scientific journals on natural products alone. Simultaneously, a number of investigators lo-
cated primarily in the U.S. and Japan began to describe their work as "marine biotechnology," following the seminal publications of Colwell (1983, 1984a,b). In retrospect, the interest of scientists in marine biotechnology was sparked primarily by the following characteristics of this new field:

- the unique physiology and metabolism of many marine organisms, notably extremophiles, from hypothermal vents on the ocean floor,

- the fascinating and potentially commercially valuable compounds produced by marine organisms, some of which exhibit highly unusual chemical structure and intriguing bioactive properties,

- the ease with which eggs of fish and shellfish can be manipulated and the results of manipulation observed, especially for commercially important species,

- the potential for exploiting the world oceans, notably diverse biological habitats, such as the coral reefs, without detrimental environmental effect, i.e., by utilizing molecular genetic methods to tap the genetic diversity through gene cloning, tissue culture, and cell manipulation methods.

Thus, marine biotechnology is experiencing significant growth in many countries of the world, especially those that traditionally have depended on the sea for food and food products. Besides work in the U.S., exciting marine biotechnology research and development is taking place in Australia, Canada, China, France, Germany, Israel, Italy, Norway, Sweden, Taiwan, Thailand, the United Kingdom, and other countries. However, both time and funding restraints allowed detailed coverage of developments only for a few foreign countries and, of these, the most important is Japan.

Japan, with its limited land mass and terrestrial resources, very naturally has directed its impressive scientific assets to the investiga-
tion of the seas that surround the country, to seek out new resources that may be profitably exploited under environmentally sound conditions, and to remediate the effects of land-source pollution. The effort that the Japanese are investing in marine biotechnology is admirable and the results they have achieved to date are impressive.

Both the Japanese government and the industrial sector of Japan realized the importance of the marine environment for economic progress and understood very quickly its value, which goes beyond simply promoting aquaculture and fisheries. The data indicate that Japan spent circa $357 million to $519 million in 1992 on marine biotechnology research and development; a sum that has increased every year since then. About 80% of this funding is supplied by industry, in contrast to the current U.S. investment pattern where government funding predominates. However, the Japanese government provides significant indirect support of industry in the form of special tax advantages, loan programs, well-funded schemes for industry-university cooperation in R&D, and regional promotional activities. The major areas of emphasis selected by the Japanese for research and development are aquaculture, marine natural products, and biosensors, although investments in environmental applications are increasing rapidly.

As a consequence of the significant scientific research and development that the Japanese have accomplished to date, with a sharp focus on discovering new marine natural products, significant discoveries have already been made. We predict that 10-15 years from now, results from these discoveries will include a cascade of new drugs derived from marine organisms and developed by Japanese scientists. These will appear in Western pharmacies and will be used to treat a wide range of infectious and non-infectious diseases, including cardio-vascular diseases, cancers, immunological disorders, and bacterial, fungal and viral diseases. In addition, it is highly probable that Japan will be the world's major source of biosensors for medicine and environmental monitoring. A smaller commercial market, in comparison to pharmaceuticals, but, nevertheless, of importance to the U.S. in terms of balance of trade, Japanese aquaculture will benefit significantly from marine biotechnology applications, espe-
cially those related to preventing and treating diseases of finfish and shellfish and marketing genetically improved finfish and shellfish species. In addition to fisheries biotechnology, Japanese scientists are focusing on advances in biological oceanography, especially the role of plankton and picoplankton in the world oceans and their effect on global climate. This work is significant and will offer benefits by the 21st century, particularly to international efforts aimed at improving the environment.

Based on our study of marine biotechnology in Japan, we believe that nation will continue promoting its marine potential. Furthermore, investment of capital from private industry will be a major factor in its successful development of new products. The Japanese effort is to be applauded because it will generate valuable scientific information and new knowledge, which will assist the Japanese in combatting their own marine pollution problems, and also elucidate oceanographic and atmospheric phenomena related to global problems, such as the greenhouse effect and global climate. It is possible that, as a result of the resources that Japanese business and government sectors are investing in marine biotechnology, by 2010 Japanese scientists will be among the world leaders in marine biological and physical scientific research and development.

In addition to basic research advances, the return on the investment in marine biotechnology will yield products of genuine value for Japanese aquaculture and their pharmaceutical and chemical industries. These successes can be predicted to occur in the mid-term, i.e., within five or ten years, and they will enhance Japan's industrial output, increasing the power of that country's already impressive and highly competitive commercial prowess.

To sum up the status of marine biotechnology in Japan, during the past decade Japan has ardently encouraged marine biotechnology at both the national and local levels. The approaches of Japan and the U.S. towards promoting marine biotechnology are dissimilar. Whereas the United States' approach has been to support basic research in areas of marine biotechnology, Japan uses a more focused, developmental approach. Since one of the primary tenants of marine biotechnology is potential utilization, and not just exploration and research for knowledge, Japanese industry will possess the world's
most advanced capabilities in many marine biotechnology applications, particularly marine natural products development, marine biotechnology to enhance aquaculture, biological oceanography, and biosensors. As has been observed: “The Japanese are now repeating their successful accomplishments in the field of electronics in the novel field of marine biotechnology” (Gibor, 1991).

Marine biotechnology in Australia and Norway can be predicted to provide advances that are likely to have significant national economic effect and will incrementally increase scientific knowledge, in general. For example, Australian investigators are probing their spectacular coastal zone, including the coral reefs, and can be expected to discover a range of marine species capable of producing chemically unique, biologically active substances. It can be predicted that some of these compounds will be useful as medicinal agents, generating profits for their developers. However, the commercial climate in Australia, which tends to be risk averse, does not appear to be conducive to the type of imaginative, long-term programs required to bring the results from marine biotechnology research to the market. Therefore, most such products are likely to be exploited with the aid of affluent foreign companies.

Based on their achievements to date, Norwegian scientists will join the front ranks of research and development in targeted areas, e.g., transforming wastes from aquaculture and fisheries into useful products, such as animal feed, industrial enzymes, and specialty chemicals. The aquaculture industry in Norway, already the world’s largest, will be positioned to utilize marine biotechnology-derived diagnostics, therapeutics and vaccines to improve its fisheries output, thereby becoming even more efficient and competitive in seafood markets worldwide. However, in view of unpredictable market conditions from increasing supply, as well as increasing competition from the growing aquaculture industry in developing countries, improvements to Norway’s aquaculture will have to become more cost effective and technologically efficient to remain at the forefront of seafood production.

An ancillary effect of the growth and development of Norwegian aquaculture is growth of other types of companies, i.e., those that offer services and products useful to aquaculture. These will be
in a powerful position to compete in sectors of the international market comprising marine animal feed, diagnostics and therapeutics. These sectors are relatively small, but are potentially lucrative and serve as entry-points for smaller biotechnology-based companies, which are likely to be a base of major economic development in the 21st century.

This study was not initiated with the intent of providing complete details of international progress in marine biotechnology, a difficult task, in view of the many research units throughout the world that now are active in this field (see Appendix 4). Instead, selected important components of the international marine biotechnology community have been highlighted. But we would be remiss if we did not mention two developments in international science promoting marine biotechnology by informing a wider audience of scientists about exciting research taking place within the field and clarifying to the public and its representatives its benefits. First, a series of major international marine biotechnology conferences have been convened, the first in Tokyo, in 1989, and the second in Baltimore, Maryland, in 1991. The third international marine biotechnology conference was held in Bergen, Norway in 1994. Second, as a sequel to a World Bank report on marine biotechnology and the developing countries (Zilinski and Lundin, 1993), the World Bank, United Nations Development Program and United Nations Industrial Development Organization sponsored the first of what will be a series of regional conferences, which was held during November 1993 in Bangkok, Thailand. Its focus was on the possibilities offered by marine biotechnology for the Asian-Pacific nations. The greatest impact is expected in the short to medium-term to be on aquaculture and natural products development.

Emergence of marine biotechnology in the U.S. has occurred in two phases, with a third on the horizon. Initiating the first phase, a small number of U.S. scientists, working largely in isolation and supported by only a few funding agencies, recognized the importance of marine biotechnology in the late 1970s and early 1980s. A significant contribution, which led to exciting scientific achievements, was to adopt the then recently developed molecular biology techniques
to marine biology. Soon a larger number of bioscientists recognized the many research possibilities the marine environment presented and proceeded to take advantage of these opportunities, which led to an initial spurt of growth in marine biotechnology R&D. During the first phase, a small marine biotechnology center was founded in North Carolina, but focused on data storage and dissemination. Two research centers dedicated to marine biotechnology subsequently were established, the first in Maryland and, shortly afterwards, a second in California. Both of these centers flourished immediately, with rapid growth ensuing.

In the late 1980s, a transition from the first phase into the second occurred. The term "marine biotechnology" began to appear, not only in scientific publications, but also in policy-related documents and government publications. The number of publications in the field of marine biotechnology increased significantly, in some areas eight to ten-fold from the early 1980s to the early 1990s. Marine Biotechnology Abstracts was first published in 1989 and has doubled in size of the publication. Two additional journals dedicated to marine biotechnology were launched, one in the U.S. and the other in Japan. Several other journals covering closely related fields, e.g., marine biodiversity and biological oceanography, and biotechnology applications have been founded in the last five years. Diverse books with marine or aquatic biotechnology included in their content or wholly or partially devoted to marine biotechnology have been published recently.

Despite these developments, as evidenced by MARBIO data, funding for marine biotechnology in general remained essentially level during 1991 and several of the preceding years. Furthermore, most of the academic and industry scientists interviewed during the time MARBIO was in development expressed a belief that the funding situation would not improve in the immediate future. Industry interest and, more importantly, investment in marine biotechnology in the United States was meager, compared to U.S. investment in biotechnology over-all. As indicated by MARBIO data, total funding for marine biotechnology research by the federal government, state governments, and industry was circa $40 million in 1992.
For purposes of comparison, this total equaled circa 7% to 11% of what the Japanese spent on research in this field. Shortage of funds in the U.S. hindered marine biotechnology from achieving the explosive growth as occurred in other areas of biotechnology.

During the second phase of development in marine biotechnology, some observers of science voiced concerns about the safety of marine biotechnology. However, after careful analysis and taking into account controversies associated with release of genetically engineered organisms to the environment, we conclude that issues related to biosafety have not been a barrier to the advancement of marine biotechnology. In fact, to the contrary, procedures already developed to ensure safety in other biotechnology research can be applied directly to marine biotechnology. As indicated by concerns expressed by environmental groups in 1990, prior to testing of transgenic carp in closed facilities in Alabama, the prospect of open field testing of transgenic marine organisms is expected to result in public debate. As occurred in other areas of biotechnology, some industries will defer from making investments in marine biotechnology, especially in development of transgenic marine organisms (see below), pending resolution of safety issues.

Several states began making major investments in marine biotechnology during the second phase. The two first significant marine biotechnology research centers, in Maryland and California, have grown significantly in size and importance. The North Carolina center, which languished for some years, finally developed into a full-fledged, state-wide marine biotechnology program. A fourth major center, concentrating on marine natural products development, was established in 1993 at the University of California at San Diego, and is active in promoting marine biotechnology in that state. Long established marine research centers, such as Harbor Branch Oceanographic Institution in Florida and the Marine Biological Laboratory in Massachusetts, have expanded their programs to include marine biotechnology and related areas. Other coastal states are augmenting their investments in the marine biological sciences, either by promoting the growth of departments in universities that already are active in the marine field, expanding the scope of existing
traditional ocean sciences centers, or establishing new marine biotechnology centers.

Despite significant advances in marine biotechnology research, some of which has produced results leading to significant applications, U.S. industry has not played a major role in marine biotechnology in the second phase. In fact, the survey of U.S. companies conducted as part of our analysis revealed that, by 1992, about 80 companies were dedicated to marine biotechnology or sponsored marine biotechnology R&D, either in-house or extramurally. The analysis of data stored in MARBIO showed that most of the effort by industry was devoted to natural products development. Nevertheless, it is a notable achievement that three pharmacological agents derived from marine biotechnology are in clinical trial, in one case, showing activity against tumors, in another, an ability to inhibit viruses and, in third, efficacy in the treatment of psoriasis. Approximately five additional compounds have shown good promise and are in pre-clinical trial. In contrast to natural products development, the aquaculture industry in the U.S. is essentially nascent, with a need for significant technological advancement to develop to its fullest capacity.

It can be postulated that at least three reasons explain the apparent indifference of U.S. industry towards marine biotechnology. First, marine biotechnology is unknown, or nearly so, to many firms. Consequences of this lack of knowledge are that these companies are not in a position to consider entering this new field and, for most companies, marine biotechnology, at best, is relatively unknown, with the perception of the working environment of marine biotechnology as being fraught with difficulties, since ocean resources have historically been viewed as being difficult to discover and, even when located, requiring strenuous efforts to exploit on a dependable and sustainable basis. Further, companies may be aware only of the relative low technological level of marine biology that existed previously, before the advanced techniques made possible by molecular biology and genetics were applied to marine-related biological research. Therefore, as explained in the body of this report, only a comparatively few companies appear to be comfortable in marine-
related research and development. Even these companies often are
unaware of the truly rich commercial potential of marine biotechn-
ology, especially in new product development.

Second, most applications within the six areas of marine
biotechnology identified in this report will come to fruition only in
the mid-term, at best, and, more likely, in the longer term. U.S. com-
panies, especially the smaller bioindustries, tend to do their planning
in three to five year cycles, thereby excluding many research direc-
tions, especially in the long range, high risk category.

Third, while we noted that the biosafety issue has not affected
the advance of marine biotechnology research significantly, uncer-
tainties remain with respect to development and production, espe-
cially for future field testing related to transgenic marine fish, plants
and microorganisms and the safety of such products in human nutri-
tion. Until these uncertainties are eliminated, most companies will
hesitate to make a long-term commitment to bring findings from
marine biotechnology to the market. However, at the same time, it
would be unwise and unproductive to revisit all the issues addressed
by the National Research Council report (United States National
Research Council, 1989) and OECD (Directorate for Science, 1992)
(Cantley, 1994).

Marine biotechnology in the U.S. appears primed to enter a
third phase, likely to be characterized by significant and rapid
growth. This conclusion is based, in part, on the expectation that the
U.S. Senate is likely to join the U.S. House of Representatives and
adopt the Marine Biotechnology Investment Act of 1993, described
in Chapter 3, thus making available significant new funding ($20
million per year for the first two years) to scientists in both private
and public research institutes and laboratories. This will, without doubt,
correct in part the problem of under-funding of this field as reported
by FCCSET and revealed by MARBIO data. We can expect new
initiatives in marine biotechnology R&D, much of which will be of
value to industry. However, the intent of the Marine Biotechnology
Investment Act would be greatly enhanced if a national effort de-
signed to produce marine biotechnology products and processes
were launched. Such an effort will produce a far greater return to
society than the uncoordinated process currently operating. Funding by Congress of the 1980 National Aquaculture Act would promote such a national effort.

From the study of marine biotechnology-related industry described in this report, four major developments can be predicted in the third phase. First, aquaculture will become increasingly important in the U.S. as technological advancement, particularly application of molecular techniques, allows this industry to expand significantly. Both basic research and industrial development of marine biotechnology, will be needed if innovations, such as closed system production for domestic aquaculture, is to be economically feasible, which it certainly can be, as demonstrated by profitable systems operating in Israel, Japan, and Norway.

Second, the most significant impact, in the short term, may prove to be marine bioremediation. Chemical and physical methods presently are methods of choice, but only for the short term. Bioremediation companies will rely on naturally occurring microorganisms, some of which will be developed for greater efficiency using classical methods for breeding and selection, in the initial phase of development of this industry. Availability of genetically engineered marine microorganisms designed specifically for bioremediation of estuaries, near shore, open coast and deep water areas of the world oceans will open new vistas for pollution remediation of the marine environment, not only oil spills, but also other toxic pollutants reaching the open ocean. As noted in Chapter 5, risk assessment schemes applicable to the marine environment and field tests of transgenic marine microorganisms are required before applications useful to the remediation industry can become reality.

Third, with development of improved screening methods for detecting a wider variety of potentially useful properties of marine organisms, more companies will be attracted to invest in R&D derived from basic research in marine biology and molecular marine biology, as well as natural products chemistry. It is envisioned that cooperative projects that partner industry and universities will increasingly be undertaken. Companies other than those interested solely in human drug development will enter into new endeavors, for exam-
ple, chemical companies interested in natural products useful as pesticides, food preservation agents, fertilizers, and other properties.

Fourth, the foregoing three practical developments will be accompanied by an equally important, if a less tangible advance, namely, the present knowledge of marine ecosystems, and their complexity and biodiversity, will expand greatly as the techniques of marine biotechnology are applied to the study of marine ecology and biological oceanography. As a result, we will gain a better understanding of how the oceans influence the weather, of the systemic effects of pollutants on the environment, of the life cycles and movements of pelagic fish, of the complex communities of marine populations such as those existing on and about coral reefs and estuaries, and of other important marine phenomena.

There is no question but that marine biotechnology has great potential. Perhaps the full flowering of that potential will be realized when its techniques are seamlessly integrated in the host of activities that constitute coastal zone development and marine resource utilization. A pictorial representation of such an integration is reflected in Figure 23, where employment of biosensors to complement remote sensing instrumentation installed on buoys and satellites, the use of bioremediation to restore waters in and around sensitive coastal environs and valuable man-made structures; application of diagnostics and therapeutics made possible by molecular biology to promote largely non-polluting aquaculture; aquaculturing of a larger variety marine animals and plants than is now possible or practicable, at times integrated with the operation of ocean thermal energy conversion (OTEC) systems, to make available for markets a wider variety of tasty and nutritious foods; and growth of pharmaceutical and specialty chemical industries based on compounds and chemicals of marine origin. Fortunately, this potential inherent to marine biotechnology is now beginning to be realized—with society the benefactor and the recipient of the wealth of the ocean’s resources.
Figure 23. Integrated ocean utilization system.

REFERENCES