

Gordon M. Cragg D. Phil.
NIH Special Volunteer, Natural Products Branch
National Cancer Institute
5117 Elsmere Avenue
Bethesda, MD 20814

Dear Member of Congress,

It is a pleasure and privilege for me to write a letter in support of the Global Conservation Act.

On December 31, 2004, I retired from the National Cancer Institute (NCI) after serving for 15 years as Chief of the Natural Products Branch (NPB). NPB is part of the NCI Developmental Therapeutics Program which is responsible for the discovery and preclinical development of drugs for the treatment of cancer. Since 1955, the Natural Products Branch and its forerunner, the Natural Products Section of the Drug Research and Development Branch, have coordinated the discovery and preclinical development of anticancer agents from natural sources. From 1960 to 1982 plants were collected mainly from temperate regions by the U.S. Department of Agriculture (USDA) through an interagency agreement with the NCI, and since 1986, the plant collections have been expanded through contracts with premier botanical institutions to cover tropical and subtropical regions. NCI has also contracted with expert marine biological organizations to collect marine plants and marine invertebrates (sponges, bryozoans, tunicates, etc.). In performing plant and marine organism collections around the world, the NCI has established collaborative agreements with 36 organizations in 30 countries. In addition, micro-organisms have been studied in collaboration with pharmaceutical and biotech companies worldwide. In all these areas (plant, marine and microbial), the drug discovery efforts have been augmented through collaborations with U.S. academic institutions and research organizations supported through NCI grants, as well as through collaborations with research organizations and universities in several biodiversity-rich countries, including Australia, Brazil, China, and South Africa.

Over 60 per cent of small molecule anticancer drugs (generally of molecular weight less than 1,000) in use today, totaling close to 100 in number, are inspired and derived in one way or another from natural products. This figure rises to over 70 per cent if one includes those synthetic products which are 'natural mimics', with properties that closely mimic those of natural compounds. While the NCI has not been directly involved in the original discovery of many of these drugs, it has played a significant role in their advanced preclinical and clinical development. Prominent among these drugs are vincristine, paclitaxel (Taxol®), etoposide and irinotecan, all based on compounds originally isolated from plants, and actinomycin, doxorubicin (adriamycin), bleomycin and mitomycin, isolated from micro-organisms. In addition, numerous agents chemically related to these drugs are in regular clinical use, and other novel agents, such as the combretastatins, ansamitocins, epothilones and staurosporines, are in clinical development. While currently only one marine-derived anticancer drug, ecteinascidin, has been approved for clinical use, many such agents, including bryostatin and dolastatin-related agents, are currently in clinical trials, and several others are in advanced preclinical development.

The discovery and development of Taxol® clearly illustrates the vital need to conserve biodiversity. It was discovered from a bark sample of the Pacific Yew tree, *Taxus brevifolia*, randomly collected by USDA botanists in 1962 from the temperate rainforests of the Pacific Northwest. Following the observation of its remarkable clinical activity against refractory ovarian and breast cancers, its development was delayed considerably by environmental concerns related to the abundance of the Pacific Yew, an understory tree which was consistently destroyed on “slash and burn” piles as part of extensive clear-cutting operations by lumber companies in the region. The discovery and development of Taxol® led to Congressional action aimed at the protection of this undistinguished understory tree, and to enlightened participation by local lumber companies in its preservation and propagation, as well as to a heightened public awareness of the value of biodiversity as a source of life-saving drugs. As testified by many cancer patients, Taxol® and other naturally-derived anticancer drugs have changed the course of their lives. Another particularly notable example is that of vinblastine which transformed childhood leukemia from a killer disease to one which is now effectively ‘curable’ in most cases.

The urgent need for global action by national and international policy makers to conserve the world’s rapidly diminishing biological resources is further illustrated by the development of novel non-addictive painkillers, such as Prialt discovered from cone snails found in seriously threatened marine habitats, and epibatidine isolated from the skin secretions of endangered tropical frogs. Even the Gila monster, familiar to the desert southwest but threatened by destruction of habitat, is the source of a novel drug for the treatment of diabetes.

While the threat to the survival of macro-organisms predominates in attracting public attention to the need for conservation, the incredibly rich microbial diversity found in all sectors of the environment, ranging from tropical and temperate rainforests to the Arctic and Antarctic icecaps, to the depths of the oceans, tends to be overlooked. Given that 100 trillion microbes are estimated to inhabit the human gut, the population and diversity of the global microbiome is beyond comprehension. From the drug discovery and health viewpoints, micro-organisms are the most prolific source of novel drugs for the treatment of many serious ailments. Microbes are the source of a host of indispensable antibiotics ranging from the penicillins to the cephalosporins and tetracyclines, to the antibiotics of last resort, the vancomycins. Well over 70% of current antibiotics are of natural origin, and one can only speculate how many millions of lives have been saved by these wonder drugs of Nature. Yet there remains a desperate need for the discovery of new classes of antibiotics to counter the increasingly rapid emergence of drug resistant strains of pathogens, such as those emanating from the common hospital pathogen, *Staphylococcus aureus*.

Microbes are also the source of the world’s best selling drugs ever, the statins, with the annual sales of Lipitor exceeding \$14 billion in 2009. While Lipitor itself is totally synthetic, the inspiration for its design and synthesis lies with the original microbial statin, mevinolin, which as lovastatin was the first of these drugs to advance into commercial use in the 1980s. Add to these blockbusters, the immunosuppressant drugs,

cyclosporin and rapamycin, which are fungal metabolites and are essential to transplantation surgery, and the anticancer drugs already discussed above, and one gets a feel for the indispensable pharmaceutical treasure house of the microbial universe. Yet, with the burning of every acre of tropical or temperate rainforest, or the destruction of coral reefs and the pollution of huge swathes of ocean, countless microbes are being decimated and lost to humankind for the discovery of better agents for the treatment of human and animal diseases.

Finally, mention has not been made of the fact that some 80% of the world's population depends on medicines extracted from Nature, primarily herbal remedies, for primary healthcare. In addition, an increasing number of consumers in western countries, including the United States, are turning to so-called complementary or alternative medicines or botanical dietary supplements, as a means of complementing their conventional treatments. With increasing environmental degradation, the source of these complementary treatments is being lost, resulting in serious health consequences, particularly for peoples living in developing nations.

In summary, Nature is a vast pharmaceutical treasure house, much of which remains unexplored. The rapid destruction and degradation of natural resources covering the whole range of global ecosystems constitutes the irreversible loss of an invaluable repository of novel drugs, essential to the continued health of countless humans and animals. The U.S. Government has been farsighted in its promotion of the exploration of natural resources for novel drugs, as illustrated by programs such as those supported by the NCI and other NIH institutes. However, with increasing environmental destruction, quick and decisive action is required by U.S. policy makers to ensure the conservation of the remaining resources for the benefit of the U.S. and global patient populations.

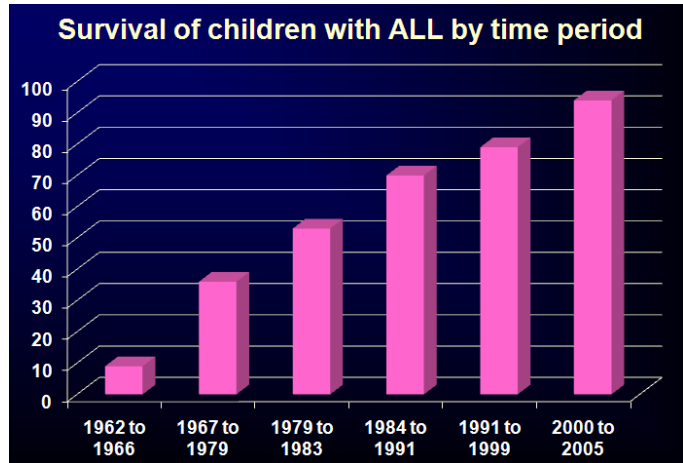
Sincerely,



Gordon M. Cragg, D.Phil.
NIH Special Volunteer
Natural Products Branch
Developmental Therapeutics Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute
Home address:
5117 Elsmere Avenue
Bethesda, MD 20814
U. S. A.
Phone: 301-564-1240 (home); fax: 301-846-6178 (office)
e-mail: gmcragg@verizon.net

Dear Colleague,

I met Isabelle Morin June 5, 2004 when she arrived as a 3-year old to St. Jude Children's Research Hospital for treatment of leukemia. As a pediatric oncologist, nothing gives me greater pleasure than to see a child like Isabelle grow up and lead an ordinary life – going to school, being with friends, trying out a new recipe, and spending time with her parents and brother. These are not the stuff of legends, but the every-day happiness that modern cancer care makes possible for 85% of children with acute lymphoblastic leukemia (ALL). Indeed, the survival of children with ALL has risen from 5% in 1960 to 90% in 2010 (see graph), due in large part to medicines derived from plants. For example, vincristine is derived from the plant *Catharanthus roseus* (a species formerly known as *Vinca rosea*) that is native to Madagascar. Had it not been for this life-saving discovery and its incorporation into ALL treatment regimens, Isabelle's outcome would have been much less certain. Developing new medicines and new ways to use them is the cornerstone of progress in oncology, so we depend on many natural sources of inspiration. Even once a cure rate of 100% is achieved, we will still need a steady supply of new medications so that treatments can be made shorter, less toxic, and less expensive.



I hope that through the proposed preservation efforts, rain forests and other biodiverse natural reserves can be preserved for the benefit of future generations, and thank you for your support for HR 4959, which will help to ensure continuous discovery of new medicines so that children like Isabelle can continue living their extraordinary lives free of debilitating illness.

Sincerely,

Scott C. Howard, MD, MSc
Medical Information Officer
Director of Clinical Trials,
International Outreach Program
Associate Member, Department of Oncology
St. Jude Children's Research Hospital
262 Danny Thomas Place
Memphis, TN 38105
Office: (901) 595-2972
Fax: (901) 595-2099
Mobile: (901) 216-1628

