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COVER STORY

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SPEAKING OUT

The Case For Natural Products Research

A. MAUREEN ROUHI, C&EN WASHINGTON

Natural products research is almost disappearing. The field is perceived as old-fashioned and unexciting: Here's another structure from an obscure organism--so what? The most interesting compounds already have been found, many people believe. If the chances for novel discovery are slim, why bother? In addition, sampling natural products outside one's national boundaries has become torturous.

Against this background, C&EN spoke with [Jerrold Meinwald](#), Goldwin Smith Professor of Chemistry at Cornell University and a pioneer in the field of chemical ecology, about the outlook for natural products research.



Meinwald
PHOTO BY MAUREEN
ROUHI

C&EN: Have most of the interesting things been discovered?

Meinwald: By no means. For flowering plants, about 250,000 species have been described, of which perhaps 10% have been examined chemically. Many were examined decades ago, when techniques were relatively crude. We can do a more thorough job and find many more interesting compounds if we pick target plants that are interesting for some reason and study them in chemical depth.

The number of insect species described is about 1 million, and many more have never been described. Most of these insects communicate or defend themselves through chemistry, and maybe only a few thousand species have been examined. As chemists, we've barely begun studying insects.

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Soil bacteria have been extremely important sources of antibiotics, and we certainly need new antibiotics very badly. However, only a very small percentage of soil bacteria have ever been cultured. That most of them are unculturable means that we must be missing a huge number of metabolites. Researchers are getting around this issue by getting DNA directly out of the soil, putting it into host organisms, and examining the metabolites expressed.

Most marine organisms probably have not yet been described. And most of those already described have not been examined chemically. Natural products from marine invertebrates often have structures unlike those of compounds from terrestrial organisms. A whole new chemical vocabulary from the marine environment has yet to be learned. We are far from understanding what these compounds do for the organisms that produce them, or what they might do for us.

C&EN: If so much can be examined, where should one begin?

Meinwald: Doing it randomly is not intellectually satisfying. It would be nice to have a biorational way to select organisms for study, and there are several possible guidelines.

Let's look at "living fossils," organisms that are the sole representative of their type, the ginkgo tree, for example. Ginkgos are an ancient species. Their relatives are long since gone. Perhaps some wonderful chemistry has preserved the ginkgo when all its relatives became extinct.

Ginkgo trees have in fact been the source of interesting natural products. The ginkgolides being studied by [Columbia University professor] Koji Nakanishi are now coming to the fore as memory aids.

In a field that has been ravaged by herbivores, some plants, although they are without protective structures, are untouched. Perhaps they are distasteful or toxic and are therefore protected against natural enemies. Very well preserved plants are likely going to be chemically interesting.

Look at insects. Many species use camouflage to evade predators, but some, such as ladybugs, call attention to themselves with brightly colored markings. Why? Perhaps to remind a bird that it vomited the last time it ate one of them. Brightly colored insects tend to have systemic poisons or defensive sprays, and they advertise it.

Other biorational ideas are possible. Chemists need to talk to biologists, who could offer valuable guidance about where to

start. Good field biologists are likely to notice interactions that might provide clues to interesting chemistry.

C&EN: How are the intellectual property issues arising from natural products drug discovery to be addressed?

Meinwald: The problem of who "owns" nature merits many hours of discussion. Right now, the concept of biopiracy is defeating many attempts to discover and develop new natural products for human benefit. The sad thing is that the problem creates conflicts even among different groups within the same country.



EAT ME NOT Brightly colored insects keep away predators with distasteful or toxic compounds.
CSIRO PHOTO

In Brazil, for example, one group of indigenous Amazonian people who felt they had not been fairly represented terminated an agreement with researchers from the University of Saõ Paulo on a project to study medicinal compounds coming from their region. Nobody benefits from this behavior. If potential new medicines are not discovered, developed, produced, and sold, no one profits. In the meantime, mindless logging continues and habitats are lost. When the species producing potentially useful compounds are consequently lost, they're gone forever. For the Brazilians, or anyone else, to fight among themselves in this way is heartbreaking.

But why look to Brazil? You can look for chemical treasures in your backyard. While it is true that the greatest species diversity is found in tropical rain forests, there is still plenty to be discovered at home.

C&EN: How has support for natural products research changed in the past 10 to 15 years?

Meinwald: The old-fashioned approach--collect, isolate, elucidate--will not excite anybody and won't get funded. Organic chemists who want to work in this area need to make convincing arguments why what they want to do is terrifically important and interesting.

As one small example, we're starting a new effort to look at spider venoms. Spiders have been examined before, but of the 40,000 described species not more than a few hundred have been studied and most of them not thoroughly. Very little is

known about the chemistry of spider venoms. What we know for sure is that all spiders earn their living by paralyzing their prey. And the neurochemical agents responsible for this activity are right in the venom. Nowadays, when you can do chemistry on a very small scale, a dozen spiders may be enough to find a novel neuropharmacological agent or to define a novel drug target.

C&EN: How else can natural products research be more appealing?

Meinwald: It's shortsighted in a way to study nature's chemistry only from the point of view of, "Can I make a drug out of it?" For some researchers, it is even more interesting to look at natural products from the point of view of their significance to the producing organisms.

It is intellectually rewarding to try to understand how these organisms are talking to each other, what they are saying, what chemicals they use to do so, how they get those chemicals, and how chemical communication systems evolved. That is basic knowledge. But the more you understand the chemistry of biotic interactions, the better you could manage forests, pursue agriculture, and avoid parasitic diseases and disease vectors and the better you could foresee the consequences of introducing new species or eradicating others.

Extraorganismal interactions make up a chemical web that keeps the environment working the way it does. With the techniques now available, chemical ecology--which is the study of the chemical interactions between organisms--is poised to look at nature in a new way. To understand biotic interactions at a molecular level is both a great opportunity and a major challenge for future chemists.

COVER STORY

REDISCOVERING NATURAL PRODUCTS

Cast aside for years, natural products drug discovery appears to be reclaiming attention and on the verge of a comeback

SPEAKING OUT

The Case For Natural Products Research

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Advanced Technologies Transform Natural Products Drug Discovery



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In natural products drug discovery, traditional, as well as novel, approaches are being applied

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