misleading targets that have beset asthma drug development in the past. Asthma is a complex heterogeneous disease in humans and the current hypothesis of its aetiology have not been adequately tested by conventional methods. Finding the underlying molecular signature holds the promise of novel disease-modifying drugs for asthma or asthmatic diseases.

Summary

Overall the conference was a dynamic interface where academic clinicians and scientists from the pharmaceutical industry could meet. Each of the talks was followed by healthy discussion and in spite of the usual problems of disclosure of company information, the current position in asthma research was clearly expressed and perhaps the way forward more clearly defined.

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Bioprospecting or biopiracy?

Biodiversity is dwindling at an alarming rate – it has been estimated that 50 species become extinct daily and it has been projected that by 2020, 15% of biodiversity will be lost (http://moby.ucdavis.edu/GAWS/122/1alfa/fpart1.htm). More than half of all plant and animal species live exclusively in the rainforests of the Third World. Deforestation through activities such as mining, timber harvesting, farming cash-crops and cattle ranching – short-term remedies to national debt – is therefore a major concern. The commercial potential of biodiversity has driven pharmaceutical and biotechnology companies to seek out and extract useful biological resources before it is too late.

More than half of the world's biodiversity resides in the rainsforests of the Third World. The exploitation of the knowledge and resources of indigenous communities must be based upon mutually agreed terms between the industrialized nations and developing countries.

Economic pressures

One economic trigger for the commercial viability of bioprospecting was provided by the decision of the US Supreme Court (*Diamond vs. Chakrabarty*, 1980) that Chakrabarty could patent a genetically engineered oil-eating bacterium because 'his discovery is not nature's handiwork, but his own'. On the strength of this decision, the US Patent and Trademark Office (PTO) began routinely granting patents on hybridized and recombinant organisms, and within a few years, micro-organisms, plants, animals, cell lines and genes were under private ownership. In 1995, the PTO issued a patent to the US National Institutes of Health (NIH) for an unmodified human cell line drawn from an indigenous person from Papua New Guinea. It was the first time such a patent has been granted and it caused international outrage.

While it is evident that intellectual property rights (IPR) are a prerequisite for businesses to protect their return on investment, some claim that the ethical issues of IPR over biodiversity, indigenous know-how and biological samples are perceived as secondary issues. The agricultural and pharmaceutical industries have pressured governments to implement the General Agreement on Tariffs and Trade (GATT) and other international trade agreements, including the Convention on Biological Diversity (CBD), and this has cemented their rights to patent the resources and

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indigenous knowledge of the Third World. This has led to accusations of legalized biopiracy – selfish exploitation of resources and indigenous knowledge.

Value of traditional knowledge

The traditional knowledge of indigenous peoples is highly valuable: it is important for both biological and cultural conservation, and it is arguably the most effective means of discovering new medicines from nature. Detailed interviews with indigenous healers by ethnobotanists identifies the most valuable plants. For example, Shaman Pharmaceuticals (South San Francisco, CA, USA) claim that ~50% of the plants collected as a result of talking to indigenous healers provide hits in screening programmes. With each interview, more medicinal applications for a particular plant become apparent, so performing only a few interviews is inappropriate. Often the same plant is used by different cultures for the same disease – Shaman targets these plants in particular. Unfortunately, the indigenous cultures are under threat from the patterns of social interaction and less knowledge is being handed down.

Utility of natural resources

Impressive statistics on the utility of natural resources emerged throughout a meeting entitled *Medicines from Nature: Scientific, Legal and Ethical Aspects* held at the Royal Society of Medicine, London, UK (9–10 June 1998). Michael Balick (New York Botanical Garden, NY, USA) indicated that of the top 150 prescription drugs sold in the USA, 57% are derived from natural resources. Most antibacterial agents (78%) and anticancer compounds (61%) available worldwide are derived from natural sources.

Tony Buss (Glaxo Wellcome, Stevenage, UK) explained how fungi provide an excellent source of bioactive compounds. However, only 5% of the estimated 1.5 million species of fungi have been categorized. José Jimeno (Pharma Mar, Madrid, Spain) described the potential of marine-derived therapeutics. Marine ecosystems represent 95% of the biosphere, and coastal regions are particularly promising because of the highly adapted species found in these harsh environments. Animals, especially venomous species, have provided a highly rewarding source of new drugs. André Ménez (Départment d'Ingéniere et d'Etudes des Proteines, Gif sur Yvette, France) discussed how the advent of protein engineering has enabled the toxic functions of many animal venoms to be elucidated and how toxin scaffolds offer attractive templates for the creation of new functions. The utility of plants is well known: of the 250,000 species of higher plant, 35,000–70,000 are used for medicinal purposes.

Given that the extraction of medicines from nature has been so fruitful, David Phillipson (University of London, UK) questioned the pharmaceutical industry's favouring of combinatorial chemistry over natural product research.

Cultural divide

Darrell Posey, Director of the Working Group on Traditional Resource Rights (University of Oxford, UK) described how many indigenous cultures view nature as an extension of their society. They do not attempt to classify and compartmentalize; for example, there is usually no distinction made between food and medicine. They have an holistic view of nature and society where the well-being of both go hand in hand. Their knowledge and culture are thus inextricably linked to the land on which they live, and life is a common property not subject to ownership. Their struggle for self-determination and rights to land and resources cannot be separated from their campaign against IPR.

According to Joji Cariño (Alliance of the Indigenous Tribal Peoples of Tropical Forests, London, UK) the IPR system constitutes a serious threat to indigenous health systems. It is perceived as a new form of colonization and a tactic by industrialized nations to confuse and divert the struggles of indigenous peoples for their rights to land and resources. Indigenous people have declared that they are willing to share their knowledge for the benefit of humanity, but demand the right to say when, where and how it is used.

International system

Resolving the diverse interests of industrialized nations and developing countries to conserve biological and cultural diversity while allowing its exploitation for the benefit of commerce and humankind is no small feat. But this is exactly what the CBD was set up to do when it was opened for signature during the Rio de Janeiro UN Conference on Environment and Development in 1992. According to Kerry ten Kate (Biodiversity Convention Officer at the Royal Botanic Gardens, London, UK), the CBD plays a central role for industry and research institutions to access genetic resources in a fair and equitable manner; it has three main objectives:

- Conservation of biodiversity
- Sustainable use of biodiversity
- Fair benefit sharing of genetic resources

The CBD recognizes that states have sovereign rights over their natural resources and that access to these resources is under national legislation. Furthermore, the CBD encourages the fair and equitable sharing of benefits arising from the knowledge, innovations and practices of indigenous and local communities. There must be mutually agreed terms for access to genetic resources, subject to prior informed consent of the State.

Countries are increasingly prioritizing the sharing of research results, participating in research, technology transfer, training and capacity building in return for access to their genetic resources. Exactly how the framework is applied is resolved by the contracting parties involved; for example, some partnerships offer help in kind, such as medical assistance and investment in local infrastructure, while others support conservation projects.

The CBD is now ratified by 171 countries and the European Union; however,

a notable exception is the USA, which is reluctant to regulate its biotechnology industry and views the requirements for technology transfer as a disincentive to develop new technologies.

The Costa Rica experience

Nicolás Mateo, General Coordinator of the Instituto Nacional de Biodiversidad (INBio) – a not-for-profit, non-governmental organization in Costa Rica established in 1989 – described the efforts made by INBio to conserve, understand and sustainably utilize their biodiversity. In Costa Rica about 25% of the national territory is protected by governmental and private entities. It is estimated that within these habitats, some 500,000 species of plants, animals and microorganisms exist, which represents about 5–7% of the world's remaining biodiversity. INBio intends to collect and classify its biodiversity and make it available through a national inventory – about 18% has been described so far. Through their Biodiversity Prospecting Program, this information and provision of chemical extracts from plants, insects and microorganisms is supplied to local and international research centres, universities and industry. Typical research agreements include a minimum 10% donation of the research budget to the Ministry of Natural Resources, Energy and Mines to help pay for the costs of biodiversity upkeep, technology transfer, training local scientists and compensation for services and information, such as species identification and sample collection and preparation. The remainder supports the in-country science and processing infrastructure and continues the biodiversity inventory. In the event that other benefits are derived from a successful research product, 50% of the royalties awarded to INBio would be donated to the Costa Rican National System of Conservation Areas and the remainder would be used to continue the INBio process.

The first major bilateral agreement for bioprospecting was made in 1991 between Merck & Co. and INBio. Mateo reported that Merck has renewed these two-year contracts twice since 1991 and that $2.6 million has been transferred to Costa Rica under these agreements.

Conservation in Africa

Inventory projects are also being carried out in the forests of West and Central Africa by the non-profit organization Bioresources Development and Conservation Programme (BDCP). Maurice M Iwu (Executive Director of BDCP, Walter Reed Army Institute of Research, Washington, DC, USA) described how, historically, Africans have not benefited significantly from either the use of biological resources found in their territories or the outcome in trade in natural products. To redress this, the BDCP has established a project in collaboration with traditional healers and local communities for the development of therapeutic agents based on traditional knowledge in which the interests of the various stake-holders are addressed in an equitable manner while conserving biodiversity. The goal is to provide communities with the tools to become self-sufficient in an increasingly industrialized world, while retaining as much of their cultural framework as possible.

Sharing the wealth

Katy Moran [The Healing Forest Conservancy (HFC), Washington, DC, USA] described the unique approach that Shaman Pharmaceuticals has adopted to drug discovery. Field research involves ethnobotanist–physician scientific teams consisting of two Shaman scientists and one indigenous healer. Working with indigenous peoples involves prior informed consent and agreement of principles and contracts. Shaman's view is that it is unethical to delay compensation for services until a drug can be developed because the needs of indigenous peoples are often urgent. It therefore has developed a three-tier system for sharing benefits – short-, medium- and long-term. Short- and medium-term reciprocity include benefits that support projects identified as priorities by the communities and organizations, such as public health, land demarcation and education. Some countries choose technology transfer as compensation.

Shaman also promises to pay a proportion of the profits from sales after a product is on the market. These long-term benefits will be equally distributed to all contributors to Shaman's drug discovery efforts, no matter where the project originated. The HFC, a non-profit conservation organization, was founded by Shaman to create and implement the return of these long-term benefits through trust funds. Shaman's first drug, SP303 (Provir) – an oral drug for diarrhoea – is targeted for launch in 1999.

Room for improvement

It is often claimed that there is an asymmetry in the returns gained from the knowledge that indigenous people have given in good faith to outsiders. For example, the $2.6 million supplied to Costa Rica by Merck over the past seven years might be considered to be loose change compared with the overall R&D program expenditure. The provisions within the CBD dealing with the financing mechanism are still largely unresolved. There is also no system for enforcing compliance of conservation obligations in developing countries.

The Rural Advancement Foundation International (RAFI) argues that, although the bilateral agreements encouraged by the CBD appear to be an opportunity for technology transfer, it actually amounts to little more than exploitation of cheap labour. The emphasis on bilateral agreements may also undermine the establishment of multinational approaches for supporting conservation and use of biodiversity, because industrialized nations are unlikely to contribute to such programmes if their transnational corporations already have access to the genetic resources they require through bilateral agreements. Multinational agreements, involving collaboration between developing countries that are in negotiation with industrialized nations for access to their biological resources will reduce the likelihood of exploitation, prevent 'bidding' wars between Third World countries to sell their resources and also

ensure a healthy global trade in biological resources.

Beyond these issues many questions and problems concerning bioprospecting remain:

- The demands of some countries may be so high that pharmaceutical companies may be deterred from accessing their resources.
- The CBD encourages bilateral agreements with nation states, but often difficulties can be encountered in using the indigenous knowledge of cultures that may be at odds with or enemies of the nation state or occupy more than one nation state.
- There are sometimes difficulties in determining with whom agreements should be made. Who are the official guardians of the knowledge? Where are the boundaries of an indigenous culture?
- Much indigenous knowledge is already published and therefore in the public domain.
- Should there be retrospective repatriation of funds for plant knowledge taken in the past?
- Accusations of biopiracy by the media could diminish the chances of success of a drug and tarnish the public face of a company. Pharmaceutical companies may view this as a disincentive to forge agreements with developing countries for access to their biodiversity.

Hope for the future

Central in the fight to conserve biodiversity is the struggle for indigenous cultures to gain self-determination. Julian Burger (UN Working Group on Indigenous Populations, Geneva, Switzerland) reported that a draft declaration on the rights of indigenous peoples has been drawn up and that within it are some provisions that refer to the use of medicinal plants and traditional knowledge. Human rights issues raised in UN talks have included the protection of ownership of indigenous knowledge. It has been proposed that a permanent forum should be established within the UN to facilitate the participation of indigenous peoples in debate on global issues.

Successful resolution of many of these issues may only be possible when developed countries can find some way to accommodate the belief, held by many traditional cultures, that nature in essence is not a commodity that can be owned.

Simon Fenwick

Alosetron in women – improving gut reactions

Results from a Phase II dose-ranging trial from Glaxo Wellcome suggest that their investigational drug alosetron can provide adequate relief of pain and discomfort for women with irritable bowel syndrome (IBS). The same trials, however, show that it does not work for men. Allen Mangel, MD, Clinical Research Director at Glaxo Wellcome in North Carolina presented the results during US Digestive Disease Week (16–22 May 1998). Mangel says the trials demonstrated that the proportion of female patients who reported relief of IBS-related pain and discomfort was significantly greater with alosetron (1 and 2 mg twice daily) than the proportion of patients reporting adequate relief with placebo. Alosetron is a selective hydroxytryptamine type 3 (5-HT_3) receptor antagonist.

Suffering in silence

Irritable bowel syndrome, also known as spastic colon and mucous colitis, is a rather common but little discussed syndrome. Some 15% of Americans are suffering, amounting to ~25 million people. With no definite cause having been identified, it is difficult to treat. Symptoms usually first appear in the mid-twenties and often include severe abdominal pain, bloating, urgency, and sporadic constipation and diarrhoea. Its cause is not fully understood but IBS has commonly been linked to neuroticism, stress, diet, genetics and even a history of abuse, especially of a sexual nature. Women tend to be more prone to the syndrome (70% of cases) than men.

The Glaxo Wellcome Phase II trials involved 370 patients in five countries. Patients were randomly assigned 12 weeks of alosteron treatment (1, 2, 4 or 8 mg) or placebo. Female patients taking alosetron reported that within the first month, not only was there relief from pain, but there was also improved stool consistency, less frequency and urgency. Some patients felt some improvement within a week. The men in the trial reported no improvements in their bowel function at all.

Therapeutic role

According to Mangel, the trial has provided positive results for a developmental drug, which is now in Phase III to confirm the efficacy of this putative drug in IBS. Moreover, the trial has also helped to define the clinical end point of efficacy for future experimental drugs for IBS, as indicated by relief of abdominal discomfort and pain rather than some previously indeterminate symptoms.

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