Unifying biology

Bernard Dixon

I was never wholly convinced, 40 years back, when my biology teachers spoke so passionately about the unity of life. True, humans share the same biosphere and have emerged from the same process of evolution as polar bears and pine trees, hedgehogs and bracken, tapeworms and toadstools, bacteriophages and typhoid bacilli. But these things look different, whether to the naked eye or under the microscope, and the words, techniques, and concepts used to portray and understand them differ enormously. This became apparent even within one superficially cohesive domain—as illustrated by moves during the 1950s to abandon the established disciplines of bacteriology, virology, mycology, and protozoology and teach the single subject of microbiology instead. A new wave of propagandists arose to preach that micro-organisms of whatever hue should be seen together as communities. Soon anyone who demurred or resisted this new orthodoxy was vilified as rather stupid. Departments, courses, and textbooks were renamed accordingly.

Then we all woke up one day and decided that there was hardly anything at all in common between the anthrax bacillus and *Penicillium*, between soil living rhizobia and blood living malarial parasites, or between the virus of poliomyelitis and the fungus responsible for South American leaf blight. Their lifestyles, their structures, the laboratory methods required to culture and study them, and the language needed to describe these varied forms of protista were poles apart. All they really shared in life was their small size. End of the enforced unity of microbiology. Departments, courses, and textbooks shifted ground again. Journals that had become interested in cross fertilising in the interests of the new paradigm began to diverge once more.

Unified language

But now, a quarter of a century on, all of this really is changing. Suddenly, the practicalities and insights that have emerged from the efflorescence of molecular biology over the past two decades are feeding into all sectors of biology, bringing a unified language and common operating procedures to formerly disparate specialties. Today medical microbiologists and plant pathologists, veterinarians and virologists, even immunologists and cardiologists, describe their prey in terms of genomes and kilodaltons, messengers and gene expression, structural homology and the matching of bioactive substances with their corresponding receptors on cell surfaces. They all know about, and many of them actually perform day by day, the sequencing of proteins, the mapping of chromosomes, and the cloning of genes.

One indication of how far these approaches have permeated and unified the life sciences was afforded by a Dahlem workshop held recently in West Berlin, which was devoted to the once pragmatic art of pharmacotherapy.* Looking beyond morphine towards the development of improved techniques of pain control the event centred on our emerging knowledge of antinociception in molecular biological terms. Already, as shown by research reviewed during the workshop, we know that opioids and opioid peptides function by interacting with three types of receptor (μ ,

δ , and κ) in the central nervous system. They can be distinguished by their differing sensitivities to antagonism by naloxone and other features such as their neuroanatomical patterns.

In the central nervous system these receptors are activated by β endorphin, the enkephalins, and the dynorphin related peptides. We understand how these peptides are related structurally and know that they are encoded by three different genes. Although slightly different mechanisms are at work, it is also clear that activation of the receptors decreases the entry of calcium into the cells.

Intense interest is now being focused on μ and κ receptor subtypes, and on recent claims for the existence of ϵ , λ , and ζ (zeta) receptors. Although one of the four Dahlem study groups described this evidence as “preliminary and therefore inconclusive,” it seems only a matter of months before we have a comprehensive perception of the molecular basis of opioid receptors. The same applies to the question of whether the same or different genes code for μ , δ , and κ receptors (and their subtypes). Several reports have appeared recently concerning the purification and even cloning of these receptors. The cautious verdict of Dahlem participants was that no opioid receptor protein has yet been sequenced. But again, that achievement seems to be just around the corner. Three highly efficient techniques have already been used to clone the genes coding for other neuroreceptors, and there is no convincing reason to suppose that opioid receptors will resist such efforts.

Progress from pain control

The purpose of all this activity is, of course, to help in the design of more effective drugs for controlling pain. At the moment even opiates, the most powerful known analgesics, fail to provide relief for a substantial number of patients who require them. Although the reason may be serious side effects, which limit the dose that can be given, and although in some other cases the doctor, nurse, or patient fears that larger quantities would lead to tolerance or addiction, there remain occasions (such as in trigeminal neuralgia) when opiates at any dose simply do not reduce a patient's pain.

The message from Dahlem was that progress in the relief of such resistant pain hinges on the cloning of receptors, the development of potent and selective agonists and antagonists for the various types and subtypes of receptor, and related advances in our comprehension of antinociception at the molecular level. Already, important steps have been taken in, for example, the chemical modification of morphine and other opiates, leading to the definition of pharmacophores corresponding to specific types of receptor. This in turn has facilitated the synthesis of potent, selectively reversible, or irreversible antagonists for μ , δ , and κ receptors.

Studies of this sort seem certain to benefit the practice of medicine. But there could be a bonus, too, in a real understanding of why the opium poppy *Papaver somniferum* should contain substances that mesh so precisely with receptors in the human brain. Now there's a phenomenon to unify biology.

Middlesex HA4 6AW
Bernard Dixon, PHD, science
writer

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