Patenting nature's secrets and protecting microbiologists' interests

THE patenting of inventions in microbiology, is arousing unusual interest the United States and Europe. **Stephen Crespi,** Patents Controller at the UK National Research Development Corporation examines recent developments in Europe

THE US Supreme Court is hearing the appeal brought by Dr A Chakrabarty in 1972 over the rejection by the Patent Office of an attempt by GEC to patent an oil-consuming strain of *Pseudomonas* obtained through genetic manipulation. And in Europe, the European Patent Office has recently changed the mechanism, called Rule 28, for ensuring public availability to third parties of new strains of microorganism deposited in culture collections for patent purposes.

The legal controversy aroused in the US by the long-running Chakrabarty case has not fully erupted in Europe because there has been no comparable test case. But Europe must view developments in the US with interest because in a world in which legal systems borrow from one another the outcome in the US may affect that in Europe.

Some of the older American decisions show judicial condemnation of attempts to patent nature's secrets where living organisms are involved — although patents were allowed for meritorious discoveries of inanimate products of nature, vitamin B_{12} being one of the most celebrated examples.

In Chakrabarty the fundamental point is simple; is a living organism which otherwise complies with legal requirements for patentability nevertheless disqualified because it is alive? In answering this question the court has to consider how to accomodate the product of genetic engineering in a patent system based on the models of classical physics and chemistry. However, if the decision of the Supreme Court later this year is limited to man-made organisms which are the result of genetic engineering it will be disappointing after so much effort has gone into dealing with the broader issue.

To put these developments into perspective it is worthwhile summarising the possible categories of patentable invention in microbiology. Microbiological processes have long been recognised by courts as suitable for process patents; and the newer patent statutes in Europe specifically refer to them. Patent claims may be presented for inventive developments of any of the methods of microbiology which serve a useful economic purpose such as improvements in culture media, culture conditions and the choice of strain used. Processes in which the sole novelty lies in the use of particular strains, especially newly developed strains, have become conventional subjects of "process-of-use" patents.

Products produced by microorganisms such as antibiotics and enzymes have for a long time been patentable in the form of product claims where the products were novel and where the patent law of the country concerned permitted the so-called product-*per-se* claim, i.e. not limited in scope to a particular process. Where the product was not new, and novelty resided only in the process of making it, it was customary to use both process claims and also, where possible, the product-by-process claim, i.e. a claim to the product when made by the particular process. However, it is with the other type of possible product claim, the claim to the new strain of microbial cells themselves, that tension has arisen between applicants and examiners. Claiming the microbial biomass as a useful end product was generally acceptable but claims directed to the new strain *per se* seem more recently to have raised the kind of philosophical objections in the Chakrabarty case.

The traditional attitude of the UK patent system towards patent protection involving the use of living matter has been cautious but attentive to the needs of industry and applicants for patents. The following principles have operated: the concept of "manufacture" as essential for patentability; the fact that many living substances can be bought and sold like other commodities; giving the benefit of the doubt to an applicant where the law was uncertain but where the decision could be tested by a higher authority if any contestant so wished. The test of "manufacture" was whether the product was itself a manufacture or could be applied to manufacture, or whether the process was technical in nature as distinct from the establishment of conditions under which the organism was developed by essentially biological laws. Long before the subject attracted public comment, yeast manufacturers took out patents for new yeast strains, presumably because the alternative of trade secrecy was non-existent where the live microorganism was itself the item of commerce. British patents were also granted over the past twenty years for other new strains, cell lines, and attenuated viruses intended for vaccines. The *Fusarium graminearum* strains intended as sources of single cell protein were patented without challenge in the UK in 1974 although held unpatentable in Eire and Australia by official ruling a few years later.

The British Patent Act of 1977 was brought in line with the European patent law of 1978 and practice should run in parallel under both systems. Recent informal discussions with EPO officials suggest that product-by-process claims to microorganisms will be accepted and that the decision on the patentability of unrestricted product claims to the strain *per se* will be taken soon. Much may depend on the circumstances of each case.

The number of patent applications on genetic engineering procedures reaching the publication stage is increasing. Once Patent Office Examiners have fathomed the extraordinary complexity of the subject there should be a spate of patents granted for techniques. It is difficult to see why recombinant DNA plasmids should be treated any differently from other chemical substances but whether claims to plasmids and transformed strains are obtained remains to be seen. What commercial value do these claims have and can they be policed inside the competitor's factory gates? We cannot yet judge the value of these to the innovators especially with so little experience of their usefulness. Therefore instead of being negative or restrictive we should explore ways in which the patent law can encourage these new areas of research.

What is the objection to patenting living matter? Some condemn it by asking where it will end and they argue that a logical extension to higher life forms supports their view. But law and logic are not identical and this argument has to overcome two objections.

The first is that one class of higher life forms is already protected, namely plants by the plant patents in the US and plant breeders' rights elsewhere. The latter are distinct from patent protection and show an interesting difference: the plant breeder can control not only the commercial marketing of the reproductive material of the new variety but also its subsequent multiplication whereas normally once a patentee has sold the product covered by the patent he cannot control it further. Secondly, patent legislation in some countries (including that of the European Patent Convention) specifically excludes patents for plant and animal varieties.

The patent law exists to benefit research and its financial supporters. If it becomes necessary to draw an arbitrary line between what living organisms are or are not patentable it is within the wisdom of judges

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and administrators of the law to do so in a way which supports technology and is generous to the inventor without harm to anyone else. Borderline cases will arise where the meaning of the terms 'plant' and 'animal' will have to be looked at closely but the constraints against patents for higher life forms are clearly built in to the present laws, at least according to the European model.

In presenting their survey of the patent law to the Supreme Court, the US judges of the lower court have approached the question on the pragmatic ground of usefulness to industry where they see no distinction between living microorganisms and chemical elements and compounds. If it is socially acceptable and desirable for pharmaceutical companies to develop new microorganisms and produce products containing living material such as "live" virus vaccines there can be no reason for restricting the patent cover available for these innovations.

To erect obstacles to patent protection is to encourage the secrecy which the patent law is designed to discourage. The patent system has in recent years become much more open especially with its emphasis on early compulsory publication of patent applications which in the past often remained confidential in the Patent Office for a long time. However, the emphasis on early publication has caused problems for microbiologists because a new strain of a microorganism must be available to third parties at the same time as publication. The European Patent Convention of 1973 set the trend on this point.

One of its regulations, Rule 28, had said that a new strain must be deposited in a culture collection before a European patent application could be filed properly and also insisted on the accessibility of the strain to others, subject to a few conditions, on publication of the application 18 months or so after the priority date. This contrasted with US and Japanese patent law where release of the strain is obligatory only when an enforcible right is obtained.

However, the European Patent Office has recently modified Rule 28. Availability of the strain to third parties can now be restricted between first publication of the application and the eventual grant of patent rights. During this time the applicant will be able to limit access to the strain to an independent expert acting on behalf of third parties but bound by certain conditions including that of not passing the strain out of his hands.

This improvement of the rule concludes over six years of effort by European industry and others to persuade the authorities that unrestricted availability of the culture before any rights are granted involves loss of control at too early a stage. This has been one of the first controversial questions tackled and solved by the EPO since it began operation in June 1978. The decision to change the rule has anticipated the UK report on biotechnology published last week (see Nature, 10 April, page 502) which strongly criticised the lack of protection under Rule 28.

Rule 28 was also updated to conform to the corresponding rule in the Budapest Convention of 1977 which provides that deposition of the strain in a single officially recognised culture collection will suffice for the individual, national procedures.

The detailed application of the independent expert idea remains to be worked out but the intention is that the expert will carry out experiments on behalf of third parties and potential opposers of the patent to test the patent disclosure and make an evaluation of the invention. The expert will be chosen by agreement between the applicant and the party requesting the strain or from an official list of recognised experts. Consequently the services of eminent microbiologists will be in demand and experts who might be willing to undertake this role are being canvassed. □

Evolving ideas

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EVOLUTION is not really in trouble, of course, it has never been healthier. It has gone into the computers. This is a sad business when one thinks of the halcyon days about a century ago. It is true that Darwin, the brooding sage, was a recluse at Down, but his supporters were having a wonderful time. We have been reminded of this in the splendid television series "The Voyage of the Beagle", and especially by the exciting re-enactment, on this programme, of the confrontation between Bishop Wilberforce and Thomas Huxley. The question asked by the Bishop was on which side Huxley claimed descent from the apes. Today we might reply that the maternal line of inheritance has a slight edge because mitochondria probably travel with ova. However, Huxley's thunderous response was directed personally at Wilberforce, whereupon it is said, a young woman fainted. Ironically, Queen Victoria, the supreme head of Wilberforce's church, carried a mutant gene for one of the blood-clotting globulins (Factor VIII), for the male haemophiliacs among her descendants provided a tragic and classic example of the ruthless effects of natural selection.

Evolution then set forth for many years on an adventure among fossils of extinct animals and plants. Pterodactyl, *Tyrannosaurus* and *Archaeopteryx* became household words. Descriptions of the bones of our ancestors were often in the news. The Scopes trial put evolution into the field of entertainment. Next, biochemists devised methods for determining the sequences of amino acids in proteins. It became possible to measure evolutionary divergence numerically in terms of amino acid differences between similar proteins in various species. Haemoglobins of gorillas, chimpanzees and human beings were distressingly similar, but widening differences were found in other species. The fun was disappearing from evolution, but worse was to come for the classical taxonomists. Incredibly rapid new methods were perfected for measuring long sequences of nucleotides in DNA, and the results, photoreduced to near-illegibility, appear in *Nature* almost every week.

A few years ago, we could examine phenotypes but we never expected to be able to read genes. Now every sequencer can become a computer-aided evolutionist. Viruses evolve just like entire organisms; in fact, genes in simian virus 40 and the polyoma virus have diverged even further from each other than genes for the alpha and beta chains of haemoglobin, which have spread far apart in the 500 million years since they separated from a common ancestral molecule. But who knows how fast viruses evolve? They leave no fossilized imprints in the rocks as guideposts of their age.

To look for a gene in DNA, you scan for "open reading frames". These are regions in nucleotide sequences that are free from occurrences of TAA, TAG and TGA: the "stop signals" in protein synthesis. It is becoming quicker to find new proteins in DNA sequences than to separate them from protoplasm. It is even possible to find genes that are no longer in use. Phil Leder recently called such a gene (for a mouse alpha haemoglobin chain) a "rusting hulk", because it had accumulated so many changes, including deletions and insertions.

All evolutionary changes result from inherited changes in DNA molecules. It is difficult to get emotional about alterations in the linear arrangement of A, C, G and T. The spiritual descendants of Bishop Wilberforce must find it rather dull to argue with computer programs.

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