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# Biotechnological Inventions and the Patent Law: Outstanding Issues

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## Introduction

Although nearly 4 years have elapsed since the last review on patent law in this series (Crespi, 1989), many of the issues previously discussed have not yet been properly resolved. Delays in the settlement of law suits can arise just as much from the tenacity of the contestants, who will go on appealing from adverse decisions in the hope of obtaining a favourable one, as from the delays inherent in the legal process itself.

Some of the legal disputes on specific patents outlined in the last review seem to have come to their natural conclusion, or at least to the point beyond which one or other party decides not to proceed, and these will be discussed later. The other kind of delay is that which comes from the political process, that is, questions of public policy as to what the law should allow or refuse to be patented in the sphere of biotechnology. This latter topic was addressed in the last review in the light of earlier initiatives of public bodies including the World Intellectual Property Organization in Geneva, which is at present inactive on this subject, and more especially the European Commission in Brussels, which is continuing its effort to forge a Directive to EC Member States to improve and clarify their national laws in this respect. The industry most affected by these public initiatives is that of agrobiotechnology, and the contentious issues can perhaps be seen as part of the wider ongoing debate over the General Agreement on Tariffs and Trade (GATT) and other matters involving the special problems of the agricultural industry and its dependant communities, which are unlikely to be solved in the short term.

This review will broadly follow the structure of the previous one and discuss some of the more crucial legal questions arising in specific patent cases.

Abbreviations: bGH, bovine growth hormone; CAFC, Court of Appeals for the Federal Circuit; cDNA, complementary DNA; EC, European Commission; EPC, European Patent Convention; epo, erythropoietin; EPO, European Patent Office; EST, expressed sequence tag; GATT, General Agreement on Tariffs and Trade; MRC, Medical Research Council; NIH, National Institutes of Health; *N*-met, *N*-terminal methionine; PVR, plant variety rights; t-PA, tissue plasminogen activator; UPOV, International Union for the Protection of New Varieties of Plant; USPTO, US Patent and Trade Mark Office.

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including law suits between industrial competitors. To place these in context, however, it will sometimes be necessary to sketch in the legal background against which current issues must be viewed. The most important features of this background are the concepts of novelty and inventiveness which underpin the structure of the patent law. A further topic concerns the question of patent scope, that is, how much of the technology can be covered by the claims of the patent based on what the inventor has actually demonstrated experimentally. Reference to the very first review (Crespi, 1985) may also be helpful for an understanding of some of these basic concepts. The second part of this review will look at the political dimension, as a part of which it will be important to discuss developments in the controversial subject of plant patents and animal patents and to address ethical issues which have come to the fore in recent times.

## Case law developments: Novelty and inventiveness (obviousness)

To obtain a valid patent and to enforce it successfully in the courts, the patent application and resulting patent must survive a number of legal tests. The first and most basic test is that the subject matter of the claims must be novel in the light of previous public knowledge. As a close second comes the requirement that what is claimed must also be inventive when judged against the same background. At the date an applicant files for a patent, therefore, the invention must not already have been disclosed to the public by others or even by the person who invented it. Previous public disclosure of an invention by an inventor has often ruined the chance of subsequently obtaining a patent for it, and there are some notorious examples of this in the field of biological chemistry.

## Novelty in patent law

Novelty has always seemed to be a simple concept to grasp. However, the question has arisen in recent years as to what sort of disclosure will torpedo a patent application which has been filed *after* the disclosure has been made public. Following a number of cases on this point in the European Patent Office (EPO), the matter has also recently been decided by the House of Lords, the highest legal authority on the interpretation of law in the UK, in a particular case which we shall refer to as the Asahi case.

### THE ASAHI CASE

Confirming the position taken by the EPO, the House of Lords has ruled (Asahi, 1991) that for a publication to be fatal to a subsequently filed patent application, it must be more than a *bare* disclosure of what is claimed in the application. The disclosure must be an *enabling* disclosure if it is to be an effective anticipation of the invention, that is, it must contain sufficient information to enable a person of ordinary skill and knowledge in the art successfully to repeat the experiment or process described. At first sight, this

ruling may seem to be of some help to those research workers who are anxious to obtain earliest possible recognition of their work through scientific publication but who are also reluctant to jettison completely the chance, which a patent gives, of benefiting from possible commercial application of their work. A full literature publication which issues before the author seeks patent protection will usually give sufficient information to be enabling in the above sense. However, there are exceptions, especially where repetition of the published work is impossible without access to novel strains of a micro-organism or other biological material and the publication does not provide this. But literature publication is not the only type of disclosure which is prejudicial to patent prospects. Any form of prior public disclosure may possibly be damaging in patent terms, including oral disclosures at scientific meetings, non-confidential information provided to visitors on conducted tours of the laboratory, and information volunteered to the press or other media. Posters at scientific meetings which effectively disclose the information in an enabling manner are a regular trap for the unwary (some readers may think that this point is being rammed home unduly, but others may not be fully aware of these pitfalls!).

The points made above apply primarily to the patent law in Europe. US law is different from European law in important respects and these differences will be mentioned later. In the language of European patent law, all such information which is made available in one way or another to the public (it does not have to be the general public, the interested public will do) is said to be part of the 'state of the art'. The law in European countries extends this principle further by also including in the state of the art pending patent applications of an earlier date, even though these have not reached the stage of actual publication. This is a sort of special case, a legal fiction designed to ensure that competitive applicants claiming the same invention cannot both have a patent but are treated on a 'first come, first served' basis.

## THE FIRST-TO-FILE PRINCIPLE

The case before the House of Lords involved the patent applications of two Japanese companies, Asahi and Dainippon, the question being which of the two applications was entitled to priority in regard to claims to certain DNA sequences. Priority in patent law is decided not only by the date of filing an application but also by the content of what is filed. This means that the application must be a proper disclosure of what is claimed. The legal detail of the case is complex, involving a number of applications filed in the UK, Europe, USA and Japan and the chronology of these is shown in *Figure 1*. But the matter boiled down essentially to the question whether the earliest application to be filed, that of Dainippon in Japan, was entitled to its date for priority purposes. The Dainippon Japanese application had merely disclosed the DNA sequence without giving any experimental detail of the preparation of this material. Asahi therefore claimed that Dainippon were not entitled to this earlier date and that Asahi's application, which was filed later and which

did contain an enabling disclosure of the preparation of the DNA, should take precedence over Dainippon's.

One of the Law Lords stated: 'if published information does no more than disclose the existence of a product which is not physically obtainable by the public that product cannot be said to have been "made available" unless and until the public has been told how it can be produced. The product is not available in the absence of an enabling disclosure.' According to another of their Lordships, to accord priority on the basis of a patent application which lacked such a disclosure 'would seem to encourage the filing of applications for "inventions" which may or may not be capable of commercial exploitation in the hope that in the ensuing 12 months something will turn up to render them patentable, such applications having the effect of preventing anyone else who may be better informed from obtaining a patent therefor.'

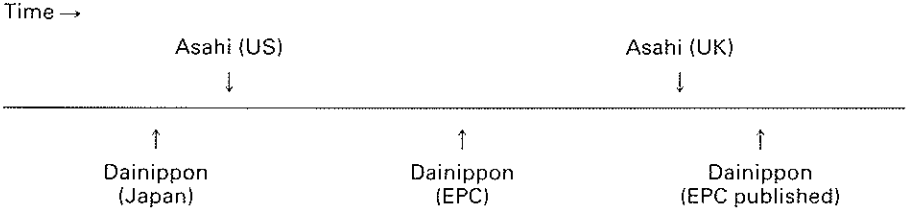
It might be argued that if a nucleotide sequence is specified, it would be obvious how to synthesize the DNA and therefore unnecessary to describe a method of preparation. The decision specifically noted that there may be cases in which the method of producing a compound may be self-evident from a mere recital of the formula, but their Lordships decided that this was not such a case. The message to applicants not to rely on such an argument is therefore rather clear – there is no substitute for doing the work and properly describing how it was done. Asahi secured their patent because they had the fuller patent disclosure.

## CONSEQUENCES OF THE ASAHI CASE

### *Legal aspects*

Although the decision seems fair, it could possibly give rise to some legal uncertainty. There may often be considerable room for doubt as to whether a prior document is enabling, since this sort of judgment involves the question 'enabling to whom?' and this in turn means assessing the degree of skill and knowledge possessed by the notional 'person skilled in the art'. The uncertainty could even be felt by the author of the publication, who might want to know whether by publishing the information the chance of obtaining a patent has been lost, and it could apply also to third parties who might want to assess their freedom to exploit the published information.

**Figure 1.** Chronology of Asahi/Dainippon applications.



*Practical effect on inventors*

Will this decision encourage research workers to be even less cautious than before about damaging their potential patent rights in their enthusiasm for rapid disclosure of information? It is not uncommon for papers read at scientific meetings to disclose results without providing an enabling disclosure of how these results could be duplicated. The Asahi case would seem to make this a respectable practice from the patent viewpoint, but it does involve skating on thin ice. Even if such disclosures do not sabotage a subsequent patent application from the point of view of strict novelty, they may undermine it in relation to the requirement of inventiveness (see later). Most patent attorneys tend to be cautious and prefer the old maxim 'file first and publish second'.

## THE FIRST-TO-INVENT PRINCIPLE OF US LAW

The patent law of the USA also recognizes the distinction between a bare disclosure and an enabling one and is in line with the European view. However, in relation to an inventor's own enabling publication, the US law is more generous than the European (see Crespi, 1989, for detail). In deciding the question of priority, the actual date of invention is taken into account and the US resident can prove this date from laboratory notebook records (however, the foreign inventor does not have this privilege). Incidentally, this is a complex area of law and the present simplified explanation is not a substitute for proper professional advice. An inventor's own prior publication will not ruin the chances of obtaining a US patent provided the US application is filed within a 'grace period' of 1 year from the publication date (this applies to all inventors who file a US application and not only to US nationals).

## INTERNATIONAL HARMONIZATION

In recent international moves to harmonize patent laws on the above issues, outlined briefly in Crespi (1989), it appeared that the USA would consider changing to the first-to-file system if other countries were willing to adopt the grace period in their laws. This proposal, along with many others, reached the stage of a Diplomatic Conference in June 1991, but unfortunately it transpired that the US Government had not received enough support at home for making the proffered change. The conclusion of a treaty was therefore postponed and is unlikely to be resumed before 1994.

A worldwide acceptance of the grace period would no doubt be welcome to the academic institutional inventors who, as a group, are prominent in biotechnology. In industry opinion is divided on this question. From experience, US industry is comfortable with the grace period, but in other countries industry is more dubious about change. Both sides must consider whether the trade-off between the first-to-file principle and the grace period is worthwhile.

Before leaving the question of novelty, special comment must be made on the patentability of those substances which exist in Nature.

### Natural product patents

Many patents have been granted for substances produced in Nature. These substances can range from relatively simple to highly complex chemical structures, the extreme form of this complexity being that of living organisms themselves, which must also be classified under this heading. Whether natural products are living or inanimate, the same considerations apply as far as patent law is concerned. Naturally occurring substances might appear to pose a problem for the concept of novelty (and inventiveness), since it may be asked how something can be patented that already exists in Nature, whether it be an inanimate substance, an enzyme, a micro-organism or higher life form, or a gene.

The patent laws of most countries make a distinction between 'discovery' and 'invention' and exclude *mere* discoveries from patentability. Some might say that the isolation of substances from Nature is mere discovery and not invention. Some might even raise the objection that because the substance already existed it cannot be new, let alone be an invention.

The product of Nature problem has a long history in patent law, but in most industrially developed countries the extraction of valuable substances from natural sources in a way which makes them available for the first time in a form in which their properties can be utilized in medicine, agriculture or any other useful art is recognized as worthy of patent protection. In terms of what belongs to the state of the art – that is, what is already *available* to the public (the true test of novelty) – these materials can be just as new and inventive as the synthetic materials created by the chemist and biochemist.

## THE US APPROACH

Most of the instructive precedents in this field have come from the US case law on purified natural products. The early court decisions pointed to the conclusion that a known substance cannot be patented as a pure product *solely* on the basis of its purity. However, where the substance was known previously only in the form of crude extracts which were of no practical use, an inventor who had devised a practically useful method of making pure product in quantity could patent not only the specific method but could claim the pure product *per se.*

The classical example of this (Merck & Co. v Chase Chemical Co., discussed briefly in Crespi, 1985) was the production of vitamin $B_{12}$ by fermentation and its isolation in bulk as the pure substance. Previously, the substance had been available only as crude liver extracts which were of no use for therapeutic application. The US District Court upheld a product *per se* claim to pure crystalline $B_{12}$. The patentee had devised a fermentation process which enabled the substance to be produced on a commercial scale and this was an unquestionably meritorious advance. Considering such a

product, the court stated that 'until . . . [the inventors] . . . had made it available to the world [it] . . . did not exist'. To object to a natural product patent in these circumstances seems to this writer to be legalistic in the extreme.

The US Patent and Trade Mark Office (USPTO) recognizes purity as a change of form from the natural material which is sufficient to justify the claim. For the discovery of micro-organisms and their isolation from natural sources, the USPTO applies the same logic and allows these to be patented if claimed as 'pure cultures'.

Two important modern examples of patents for purified natural products (Scripps Clinic and Research Foundation v Genentech, and Amgen Inc. v Genetics Institute) were discussed in Crespi (1989). The first of these involved Factor VIII, the blood-clotting factor important in the treatment of haemophilia, and the second erythropoietin, the hormone which stimulates the formation of red blood cells. These patents disclose particular chromatographic methods of purifying or isolating the protein. However, the claims are not limited to products produced by these methods; they also cover the proteins defined solely in terms of units of activity, a parameter connected with the degree of purity which these methods have made possible.

## FACTOR VIII LITIGATION

In the Scripps case, the crucial claim of their US Re-issue patent 32,011 was: 'A human VIII:C preparation having a potency in the range of 134 to 1172 units per ml and being substantially free of VIII:RP'. Scripps asserted that this claim was infringed by the defendant's manufacture of recombinant Factor VIII, since the latter would fall within its purity criteria. The defendant argued that this claim should be interpreted in the context of the Scripps method of purification and therefore limited to material purified from natural sources. The case went before the District Court of Northern California on a motion for Summary Judgment (a procedure for obtaining a speedy decision preliminary to a full trial), and in 1987 the court decided in favour of Scripps on this issue. However, on appeal to the Court of Appeals for the Federal Circuit (CAFC), it was decided in 1991 that this and the other issues in the case were too complex to be resolved in preliminary proceedings. The CAFC, therefore, remanded the lower court's findings for full trial. At the present time, the trial is still pending.

## ERYTHROPOIETIN LITIGATION

In the Amgen case, Genetics Institute Inc. had obtained US patent 4,677,195 for a method of purification of epo from human urine by reverse phase high-performance liquid chromatography. But the patent also has broad product claims, including the following: 'Homogeneous erythropoietin characterised by a molecular weight of about 34,000 daltons on SDS PAGE, movement as a single peak on reverse phase high performance liquid

chromatography and a specific activity of at least 160,000 IU per absorbance unit at 280 nanometers.'

The dispute in this case involves issues similar to those in the Factor VIII case. For similar reasons, the US court of first instance held that Amgen's recombinant product infringed GI's claim to the purified protein. However, this holding has been suspended on appeal.

The two instances outlined above are examples of conflict between the respective proprietors of a natural product patent and a recombinant DNA patent in which it has to be decided who is free to operate commercially with the recombinant protein. In these two examples, one question for the court is whether a patent based entirely on the purification of the natural product can be permitted to cover the protein as made by recombinant methods. Unfortunately, single issues are rare in patent lawsuits and the answers are often complicated by other factors. It seems possible that the US courts could still affirm in principle the dominance of the natural product patent.

## THE EUROPEAN APPROACH TO NATURAL PRODUCTS

The European Patent Office analyses this question in its Official Guidelines (EPO 1992) as follows:

> To find a substance freely occurring in nature is also mere discovery and therefore unpatentable. However, if a substance found in nature has first to be isolated from its surroundings and a process for obtaining it is developed, that process is patentable. Moreover, if the substance can be properly characterised either by its structure, or by the process by which it is obtained or by other parameters and it is 'new' in the absolute sense of having no previously recognised existence, then the substance *per se* may be patentable. An example of such a case is that of a new substance which is discovered as being produced by a micro-organism.

The Guideline speaks of products having no previously recognized existence and it is therefore rather limited. Much research in the natural product field is concerned with active substances which are known to exist, the object being to isolate the substance in highly pure form or to devise synthetic methods of producing the substance. The most topical example of this is the preparation of pure proteins by recombinant DNA methods.

### Inventiveness in patent law

Of all the concepts of patent law, inventiveness is perhaps the most difficult to apply in practice. The subject matter of a patent is said to involve an inventive step if it is not obvious to a worker of ordinary skill in the art in the light of what is publicly known at the relevant date. This formulation is almost universally accepted and intended to be of assistance, although it does little more than transfer the difficulty to the term 'obvious', which itself then calls for interpretation.

## WHAT IS OBVIOUSNESS?

The notion of obviousness is usually explained as one of simple or logical progression from what has gone before. In the research laboratories of academic institutions and of the science-based industries, it is common to pursue particular lines of investigation because they are the obvious paths to take in the search for new understanding or the solution of practical problems. This is one purpose of all scientific training. Patent law reflects this assumption in the concept of the 'ordinary person skilled in the art' who is supposed to be capable of pursuing such investigations from a common stock of skill and knowledge which can be exercised without drawing upon any inventive faculty. Such persons are expected to possess a certain level of scientific deductive power and to make practical use of it in their daily work.

Inventiveness calls for something more than the application of the foregoing qualities, but what that extra amounts to cannot be readily defined. Although the exercise of scientific deduction is often involved in the innovative process, it is not to be equated with inventiveness as understood in patent law. Patents have not hitherto been intended as rewards for scientific ability, nor are they given to research workers in recognition of their being gifted experimentalists.

The degree of inspiration required to support a patent on the ground of inventiveness cannot be easily stated in a general way, but must be assessed in every specific case on its own merits. An element of subjectivity must therefore enter into the process of judging inventiveness, but this ought to be minimal. The patent system would lose credibility if the courts of different countries were frequently to reach conflicting conclusions on equivalent patents litigated in their national jurisdictions.

## RELEVANCE OF THE CLAIMS

In determining whether an inventive step has been taken, the claims of the patent are crucial. No matter how ingenious the practical details of the invention described in the inventor's examples of the process or the specific illustrations in the patent drawings, what has usually counted is the way in which the invention is claimed. The claims can easily go beyond the inventive step and be unduly broad. Over-claiming may be a result of faulty professional judgement or may be due to the demands of a covetous applicant. If this is not forestalled at the application stage by the critical examination of the Patent Office, it may sooner or later be subjected to kill or cure treatment in litigation.

Where a patent is for a new chemical substance, the usual form of claim recites the chemical structural formula of the compound. It may be difficult to see how a chemical structure *per se* can be said to be inventive, especially where it differs only slightly from a known structure. Even where the difference is more striking, one might ask what this has to do with inventiveness. The answer lies in the properties which flow from the structure in an unpredictable manner. Inventiveness is therefore a combination of a structure

and an unexpected utility or degree of utility. For this reason, the patent is granted for the product *per se*. The inventor must describe a way of making the product (one will suffice), but the claim is not restricted to that particular method of manufacture.

A more restricted form of claim, the 'product-by-process' claim, is used when the product can only be defined by the way it has been made. In the UK and a number of other countries, this form of claim is still available when the product is not new – that is, it has been made before by older methods – and the invention resides primarily in a new process for making it. European and US patent case law have virtually ruled out the product-by-process claim for known compounds, but under both systems the protection given by a process claim extends to the product of the process. These considerations of claims to chemical substances apply equally to large molecules including proteins and nucleic acids.

## OBVIOUSNESS IN UK LAW

In English law, obviousness is considered to be a question of fact to be determined against the technological background or 'state of the art' at the time the patent application is filed. This determination usually requires taking the testimony of experts as to the state of knowledge which the competent person in the particular field is expected to have at the application date or priority date of the patent application. Expert evidence can go almost to the point of clinching the matter, but the court reserves to itself the right to decide the issue. Considering the demands made on the judges in grasping the deep technicalities of the many 'high-tech' patents that come before them, it is remarkable that the system works as well as it does.

UK case law shows that the question of obviousness can arise in different ways. First, the subject of a patent may be plainly obvious in the sense that the prior art falls just short of but nevertheless points towards what is claimed either directly or by strong implication. Secondly, even in the absence of specific pointers in the prior art, it may have been 'obvious to try' to make the claimed product or to carry out the claimed process. A third category is that of the 'obvious desideratum', where the claim defines something that everyone would like to have if only they could actually achieve it. This third category includes the case of the 'problem claim', in which the claim states only a problem to be solved but not the solution itself.

In the field of chemical inventions, the classical approach to the question of obviousness in UK law was first formulated as the celebrated 'Cripps test' (Sharpe & Dohme v Boots Drug 1927). The case involved the question whether, in order to manufacture certain higher alkyl resorcinols, it was obvious to use a process which was already known for making the lower alkyl homologues. As counsel for the patentee, Stafford Cripps put the issue as follows:

> Was it for all practical purposes obvious to any skilled chemist, in the state of chemical knowledge at the date of the patent (which consists of the

literature available and general chemical knowledge), that he could manufacture valuable therapeutic agents by making the higher alkyl resorcinols by the condensation and reduction processes described?

The court answered this question affirmatively because to establish antibacterial properties in the higher members of the series and to use a method of preparation known for the lower members was no more than *mere verification* of what was reasonably predictable.

An important later case in the *obvious to try* category (Johns Manville Corp 1967) involved the new use of a known material. Here the claim was to the use of polyacrylamides as filtration aids in the making of asbestos cement articles. The same materials had previously been used in a similar way for filtering minerals, industrial waste and the processing of clay materials. The court concluded that in order to show the obviousness of a claimed process or use, 'it is enough that the person versed in the art would assess the likelihood of success as sufficient to warrant actual trial'. The claim was for this reason held invalid in this instance. The argument that something was obvious to try will therefore fail unless there would have been a strong presupposition that the trial was likely to succeed.

The Cripps test was later adapted by the High Court in a pharmaceutical case (Olin Mathieson v Biorex 1970) involving the replacement of the Cl substituent in the structure of a known drug (chlorpromazine) by the $CF_3$ group (leading to trifluoroperazine). The question was modified to include the notion of obvious to try and re-stated as: 'Would the notional research group . . . be directly led as a matter of course to try the $CF_3$ group in place of Cl . . . in the expectation that it might well produce a useful alternative or a better drug.' This time a negative answer was given.

The test was elaborated further in a microbiological case (American Cyanamid v Berk Pharmaceuticals 1976), in which the claim was to the use of *Streptomyces* strains which would produce tetracycline without co-producing the unwanted chlortetracycline. The question (paraphrased here) was whether the notional research group would, from prior knowledge, be directly led to try to find or induce a novel strain descended from the type strain A-377 and which would have the desired properties. On this occasion, the court gave an affirmative answer, even though the search for the strain was not certain to succeed.

## OBVIOUSNESS IN US LAW

In US legal thought, obviousness is said to be a question of law, although based on certain factual enquiries. There is an extensive case law on this subject, but it will suffice here to reproduce the oft-quoted passage from the leading case (Graham v John Deere Co 1966):

> . . . the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or non-obviousness of the

subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc may be utilised to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or non-obviousness, these enquiries may have relevancy.

The US courts have stressed repeatedly that *obvious to try* is not the standard test, since many things may be obvious to try in a general sense and yet the prior art may give no guidance as to the specific path along which success will be found. There may be obviousness even though absolute predictability of success was lacking. Unexpected results can show that what was apparently obvious was not obvious in law after all. What is required to show obviousness is that there was a reasonable expectation of success.

### OBVIOUSNESS IN EUROPEAN LAW

The European Patent Office was the first and is still perhaps the only Patent Office to offer guidance on this difficult topic (EPO 1992):

> The term 'obvious' means that which does not go beyond the normal progress of technology but merely follows plainly or logically from the prior art i.e. something which does not involve the exercise of any skill or ability beyond that to be expected of the person skilled in the art.
>
> It should be remembered that an invention which at first sight appears obvious might in fact involve an inventive step. Once a new idea has been formulated it can often be shown theoretically how it might be arrived at, starting from something known, by a series of apparently easy steps. The Examiner should be wary of *ex post facto* analysis of this kind. He should always bear in mind that the documents produced in the search have, of necessity, been obtained with foreknowledge of what matter constitutes the alleged invention. In all cases he should attempt to visualise the overall state of the art confronting the skilled man before the applicant's contribution and he should seek to make a 'real life' assessment of this and other relevant factors.

#### Inventiveness in biotechnology

In classical microbiology, the prototype invention is the isolation or development of living organisms from natural sources. Here, the question of inventive step ought to be relatively uncontroversial. Assuming the inventor has for the first time isolated or produced, say, a new strain of micro-organism which is superior to known strains in some commercially significant respect, there cannot be any real doubt that he or she is justified in obtaining a patent for it. One might say that it is obvious to search for new strains, but it can hardly be said that the particular new strain for which protection is sought would have been obvious. This type of invention is one in the 'lucky find' category and so long as the strain performs as stated such a patent ought to be

water-tight. Patents of this kind are fairly easy to read and understand and the nature of the inventive step is easy to perceive.

## RECOMBINANT DNA PATENTS

To move from patents in the field of classical microbiology to those in the recombinant field is to enter a different world, populated by a new species of patent literature. For many of these patents dealing with the production of known proteins ('first-generation products'), such as the therapeutically important serum proteins, one often finds an introductory presentation of the following type:

1. Protein X is a substance of therapeutic importance.
2. Protein X is obtained from natural sources in minute amounts.
3. rDNA technology is now in place and offers the prospect of producing protein X on a commercial scale.
4. It was difficult to do it but we have succeeded in doing it.
5. Our invention provides 'a DNA sequence coding for protein X' (and sometimes 'recombinant protein X' as well).

A recombinant DNA patent for products of this type will typically describe the isolation or construction of the DNA which codes for the protein, followed by the insertion of the DNA into the vector and transformation of the host micro-organism. The patent disclosure will typically give a dictionary of technical terms, flow-sheet drawings of cloning strategy, and an impressive but densely detailed description of the experimental protocol. It is in the experimental section of the disclosure that this new kind of patent drafting is most characteristic, being so full of references to methods taken from the scientific literature as to justify a long reference list. Such lists are of course standard for scientific papers, but have hitherto been most rare in patents. Indeed, many patents of this type are 'mini-textbooks' which even include a table of contents! As noted in Crespi (1989), the patent claims will be typically selected from the following types:

(a) Recombinant protein products (and alleles, variants, derivatives).
(b) DNA sequences coding for the products of (a).
(c) Vectors containing the DNA sequences of (b).
(d) Micro-organisms, cell lines and other organisms transformed with vectors (c).
(e) Processes for constructing the micro-organisms, etc., of (d).
(f) Processes of producing products as in (a) by expression of DNA sequences (b) in a recombinant host organism.

What signposts have the courts given us to evaluate levels of inventiveness in technology of this kind?

## APPROACH OF UK COURTS

The British case on tissue plasminogen activator (t-PA) (Genentech v Wellcome 1989, UK patent 2,119, 804 discussed in Crespi, 1989) is a prime example of reliance on a claim of type (a) listed above. The patent contained a number of such final product claims of which the following is representative for purposes of discussion: 'Human tissue plasminogen activator as produced by recombinant DNA technology'.

For commercial purposes, this type of claim was exactly what was wanted, but it failed on legal grounds, being held obvious, first, because a product of this kind was a known desirable objective and, second, because the product was obtained by using known methods of gene cloning. This case is therefore a modern prototype of the *obvious desideratum* category and it allows the conclusion that, for the British courts, being first in the race to clone and express genes coding for known proteins is not enough to support so broad a legal monopoly in such circumstances.

Genentech had relied heavily on the fact that they were the first to discover the DNA sequence coding for human t-PA and to deduce the amino acid sequence of the protein. Prior to their efforts, the absence of sequence information was 'the one log holding up the log jam' in the recombinant route to this product. The Court of Appeal was not persuaded by this argument. In its view, the determination of a sequence was an act of acquiring knowledge and therefore a discovery rather than an invention. Since the recombinant methods used to apply this information were assessed as conventional for the skilled person at the priority date (May 1982), they did not add anything of inventive character to the process as a whole. One can only speculate on the judgment that might have been delivered had the methods used by the patentee been considered more original by the court.

Some commentators have considered the decisions of the UK Patents Court and Court of Appeal to have been unjustifiably severe in overturning a patent on a product of great potential medical importance. The importance of the legal issues would certainly have merited an appeal to the highest UK court (House of Lords), but this was not made. However, the lower court decisions lie squarely in the tradition of the British courts in approaching the question of obviousness in biological chemistry. The t-PA product was clearly a good candidate for production by these techniques judging by the fact that the subject of the claims was formulated conceptually as a worthwhile project long before any laboratory work was started. The patent itself made it clear that recombinant methods were perceived as an effective way of making large quantities of t-PA, even though the path might be tortuous, and that the invention was based on the discovery (some might say verification) that the technology could be successfully applied to it. Recombinant t-PA, as such, and viewed as a product, fell into the obvious desideratum category.

It should not be thought that the decision of the UK court was conditioned solely by the fact that the claims of main interest were of the final product type. The legal analysis would have been no different for claims of the type obtained in the corresponding US patent 4,766,075. The latter has no claims

to the recombinant t-PA protein but relies on claims of types (b), (c) and (d) noted above, for example, 'A DNA isolate consisting essentially of a DNA sequence encoding human tissue plasminogen activator'.

However, it must be stressed that as a precedent the UK decision applies only to first-generation products. As regards next-generation products of the t-PA type, numerous patent applications are now in the pipeline for modified or mutant forms of natural t-PA. It is clear that patent prospects are reasonable for these compounds.

## APPROACH OF US COURTS

The US Court of Appeals for the Federal Circuit have given a clear signal on the question of obvious to try (In re O'Farrell 1988) in the biotechnology field. The crucial prior art against the applicants was one of their own prior publications in the scientific literature. Had it succeeded, the application could have given rise to a patent of basic importance. It would have protected the 'fusion protein' method in genetic engineering, according to which a heterologous (foreign) gene is inserted into a micro-organism and tacked on to one of the micro-organism's homologous (indigenous) genes so that the protein-synthesizing machinery of the cell expresses the indigenous protein linked with the desired foreign protein.

The applicants' scientific paper had described the essentials of this fusion method except that the tacked-on frog DNA gene used in the paper coded for ribosomal RNA, which is not normally translated into protein. However, the authors had speculated as to the possibility of applying the method to the case of an RNA which was translatable into protein. The applicants argued that there was significant unpredictability in molecular biology at the date of the publication and it was not yet certain whether a specifically desired protein could be produced in this way. They asserted that the Patent Office rejection was based on the impermissible 'obvious to try' argument. But the court refused to accept this submission. From their own 'pioneering' paper, especially when combined with another item of prior art, there was a reasonable expectation that the method would be successful when applied to the making of proteins. By their publication, therefore, the applicants had foreclosed themselves from obtaining a patent.

In a further phase of the US litigation on erythropoietin (Amgen Inc. v Chugai Pharmaceutical Co. 1989), the validity of the Amgen patent was attacked. The patent contained a variety of claims to DNA sequences but no process claims for making the final recombinant product and no final product claims. One of the DNA claims was to 'A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin'.

As to inventiveness, the Massachusetts District Court reviewed the course of the research by Amgen and others from 1981 onward into the cloning of the erythropoietin (epo) gene. This was not a large gene and for this reason was seen in 1981 as a good candidate for cloning. But it took 2 years of painstaking work by the Amgen inventor before the successful strategy for

achieving the result was worked out. This entailed determining the correct amino acid sequence of sufficient portions of the protein structure to enable oligonucleotide probes to be designed which would extract the gene from a genomic library. A large number of probes were constructed and it was necessary to use a combination of probes which would hybridize to different parts of the gene. The great magnitude of the task cannot be denied. Genetics Institute, Cal-Tech and Biogen had also embarked on the quest for this gene.

Here there seem to be some similarities to the t-PA case. The gene was a good candidate for cloning and a number of competitive groups were pursuing it along their own trails. But apparently there were important differences from the t-PA development. First, the epo protein was an exceptionally scarce material when the Amgen inventor started work, a fact which made sequence information that much more difficult to obtain. Second, and of greater significance, was the fact that by 1981 and even 1982 there had been little or no precedent in the screening of a genomic library using two sets of probes. The court therefore concluded that it was not within the power of one of ordinary skill in the art to reduce this invention to practice at that time.

Although the court did not say so in so many words, it might be fair to suggest that recombinant erythropoietin, as a desirable product, might have been *conceptually obvious* but that its reduction to practice was far from obvious. In approaching the question of the inventive step, the US court did not put the partial sequencing of epo into a separate category from the steps which followed. The correct sequencing and the consequential design of two sets of fully degenerate probes from different regions of the sequence to explore a genomic library amounted to an inspirational combination in the eyes of the court. The court concluded that 'the unique probing and screening method employed in isolating the EPO gene was what distinguished the invention from the prior art'.

In the decision on appeal the CAFC noted that it was the product that was claimed and not the process, but decided to follow the approach of the lower court and the parties to the litigation. The point was therefore bypassed.

## APPROACH OF EPO BOARDS OF APPEAL

In the European case law of the EPC in the biotechnology field, the most prominent of the controversial issues to have arisen to date have involved questions of sufficiency of disclosure, adequacy of support for broad claims, and clarity in claim language. There has been no decided case on inventive step of the calibre of the t-PA case in the UK and the erythropoietin case in the USA. Incidentally, the European patent (EP 148,605) equivalent to the US epo patent discussed above has so far survived a formal Opposition filed by six industrial Opponents in the EPO.

The EPO Boards of Appeal have given highly favourable consideration to the early applications filed in this field and in which these difficulties have been raised, either by the EPO Examiners or in Opposition proceedings. The first example was one of the earliest and broadest scope patents in the field of

genetic engineering (Genentech I, T 292/85). The invention was typified by the main claim directed to a recombinant plasmid, the most important features of which were the presence of a homologous regulon and a heterologous DNA coding for a desired polypeptide and in proper reading frame. The principal item of prior art was the paper which figured prominently in the O'Farrell case mentioned above. This had shown the use of the claimed homologous/heterologous combination to produce a transcript which would not have been translated into protein, coupled with a speculation as to the possibility of expressing eukaryotic DNA in bacteria. Despite this, the Board found generously in favour of the applicant on the issue of inventive step, and by somewhat tortuous reasoning decided that the prior document actually pointed away from the claimed invention.

The most important point of this case as a valuable precedent concerned the question of scope of claim. The Examining Division had objected to the use, in the claims, of the broad functional terms 'bacteria, regulon, plasmid etc', arguing that these should be limited to specified known materials in order to meet the requirement of sufficiency and to avoid covering future inventions or discoveries of new materials falling within these broad descriptions. The Board rejected this view and held that for this particular invention only the use of such functional terminology could give fair protection.

In one recombinant DNA application which failed on the ground of 'obvious to try' (Monsanto, T 249/88), the application claimed a method of increasing the yield of cow's milk by administering a recombinant pituitary bovine growth hormone (bGH) having an *N*-terminal methionine group (*N*-met bGH) instead of the natural bGH as in the prior art. One prior document contained a suggestion to use a recombinant bGH for this purpose and another, dealing with the human analogue, expressed lack of surprise that the terminal *N*-met group did not affect the activity of bGH (for growth promotion in rats).

Declarations from three scientific experts were filed to show lack of predictability of the activity of *N*-met bGH in the cow from the prior art. The Board held that 'inventive step is not assessed from the viewpoint of the outstanding but cautious scientist reluctant to make a prediction but from that of the notional skilled person of average ability and knowledge'. The inability to predict, in the strict scientific sense, or the necessity to confirm experimentally that *N*-met bGH would increase milk yield, did not make the claimed method un-obvious. There were clear hints from the prior art and the results could reasonably have been expected even though experimental confirmation was necessary. The patent was therefore refused. In latching on to the idea of 'reasonable expectation' of obtaining useful results, the EPO Board is clearly in line with UK and US precedents.

### THE BIOGEN ALPHA INTERFERON CASE

Crespi (1989, p. 232) gave an account of Biogen's success in defending their European patent for recombinant alpha interferon against formal Opposition by nine industrial Opponents. Among the important points in this decision

one must be singled out for further comment in view of its significance to the relationship between patents and scientific publication. As will be clear from the above discussion of the Asahi case, and as also explained in Crespi (1985, pp. 19–20), one of the crucial concepts of patent law is that of *priority date*. The filing of a patent application creates a priority date for what it discloses. This date is obviously significant in disputes between rival applicants for the same invention. But its main significance is that it defines the line between what is prior art and what is not. Consequently, an inventor who has filed an application will normally be told that it is then safe to publish the work in the journals, the reason being that any publication coming out after the priority date cannot torpedo the patent application. This rule applies to the 100 or more countries (members of the Paris Convention) which have agreed that a patent application filed in any one country establishes a priority date which will apply also to corresponding applications filed within the following year in the other member countries. Consequently, if soon after filing the original (priority) application the inventor chooses to publish in the journals during the year before filing abroad, the publication will not harm the foreign applications.

## THE PRIORITY DATE QUESTION IN THE BIOGEN CASE

Biogen had claimed the priority under the Paris Convention of three earlier applications (I, II, III) covering DNA sequences, each of which represented a stage in the development of the invention during the year preceding the European filing. The inventors had followed the policy of publishing the subject matter of each of the three applications in the scientific literature soon after it had been filed, rather than suspending publication until the final European application had been lodged at the EPO.

The Opposition Division had held that scientific publication of the subject matter of application I prior to the filing of application II had made that subject matter part of the prior art citable against any of the final claims which were only entitled to the priority of application II or subsequent applications. As a result, certain claims which were entitled only to the priority of application II were held lacking in inventive step over the scientific publication of the subject matter of application I. However, the EPO Technical Appeal Board rejected this view and decided that so long as the publication of the subject matter of application I did not go beyond the content of the application, it could not be used against any claim in the latter application.

In effect, therefore, the filing of a patent application before publication of whatever is disclosed in the application not only protects the subject matter of that disclosure in itself, but also removes it from the realm of material which can be cited against subsequent developments of that disclosure which are protected by filing a further patent application before they are themselves published. In enunciating this principle so clearly for the first time, the Technical Board of Appeals has laid a milestone of major significance. Being of general application, this must be assessed as one of the more progressive judgments of recent years. It is highly favourable to that group of inventors

who accept the value, even the necessity, of filing patent applications, but for whom early scientific publication of research results is equally necessary for career advancement or for reasons of scientific or public interest. Unfortunately, however, the Biogen decision is not popular with those who hold a strict 'purist' view of the law and the President of the EPO has referred the decision for review by the Enlarged Board of Appeal of the EPO. At present, therefore, the point of law cannot be regarded as entirely certain; it might also be raised before national courts. If international harmonization were to result in the widespread adoption of the US grace period, the problem would disappear.

## HYBRIDOMA TECHNOLOGY

Crespi (1989, p. 234) discussed the Hybritech case, one of the earliest cases on monoclonal antibodies to go before the US CAFC. This court is the highest authority for patent cases below the Supreme Court itself. In brief, the issue was whether at the relevant date it had been inventive or obvious to substitute monoclonals for polyclonals in a known type of sandwich assay. After a thorough examination of the inventors' notebooks and the various articles published by others predicting the widespread applications of monoclonals following their first appearance in 1975, the CAFC decided that at the date of conception of this particular invention (early 1979), it was not obvious to make the substitution. Many of the published articles were dated after the conception date and in the year preceding the filing date of the patent application (therefore not damaging prior art), while the others were mere 'invitations to try' monoclonal antibodies in immunoassays without saying how this would be achieved (thus the court rejected the 'obvious to try' approach).

The Hybritech case had been preceded by a decision of the US Patent Office (Ex parte Old 1985) allowing a claim to monoclonal antibodies to malignant human renal cell antigens. The Examiner had argued that polyclonals to surface antigens of malignant melanoma cells being known, and polyclonals to human renal cell antigens being also known, it was obvious to make monoclonals to malignant human renal cell antigens by the Kohler Milstein technique. The Board of Appeal said: 'We cannot subscribe to this rationale . . . hybridoma technology is an empirical art . . . no expected results can thus be said to be present'. If making monoclonals to cancer antigens was routine and predictable, the Board considered that 'cancer immunology would have produced cancer cures'.

Against the above background, the unsuccessful 10 year struggle of Cetus to obtain a US patent for hybridomas producing monoclonals to human fibroblast interferon stands in sharp contrast (Ex parte Erlich 1992). This time the US Board of Appeals supported the Examiner's rejection based on obviousness. By 1980, the Cetus invention date, the Kohler and Milstein method had been successfully applied to the construction of hybridomas secreting monoclonals to a wide variety of antigens including human leukocyte interferon. The Board rejected the Cetus argument of 'unpredictability',

brushed aside the Hybritech and Old decisions as based on different factual situations, and concluded:

> Therefore one of ordinary skill in the art at the time of the present invention, recognising the antigenicity of the human fibroblast interferon and its potential therapeutic value, would have had ample motivation to make monoclonal antibodies to this protein using the classical Kohler and Milstein hybridoma technology. Such a person would have entered this venture with a reasonable expectation of success given the large number of successes other researchers had at that point in time in adapting hybridoma technology to other antigens.

US commentators (McGough and Burke, 1992) have asked whether the Erlich decision signals the end of monoclonal patents. While concluding 'probably not', McGough and Burke point out that Examiners will undoubtedly start to rely on Erlich as a precedent for rejecting applications. To overcome such rejections, it will be necessary to be able to point to some inventive feature of the technique used or to some novel specificity in the product.

Also in contrast to the US Hybritech approach, in the EPO case of Unilever PLC v Boehringer Mannheim (T 499/88, immunoglobulins), the Technical Board of Appeals held that the replacement of polyclonal antibodies by monoclonal antibodies in an immunopurification process required no inventive step at the priority date of the opposed patent (February 1981). The Unilever claims were to a process for the recovery of immunoglobulins of high purity and potency from milk by selective binding to a low-affinity monoclonal antibody specific to one or more of the immunoglobulins and itself bound to an insoluble carrier material. It was clear that the novelty lay only in the use of monoclonal antibodies in substitution for the prior use of monospecific polyclonal antibodies in the same basic process. This substitution was held to be the 'next logical step' and the 'desired logical and obvious step' to improve the purification process of the nearest prior art.

## POSSIBLE CONCLUSIONS REGARDING INVENTIVENESS

The litigated applications and patents discussed above represent only a fraction of those being filed and granted across a wide field, ranging over pharmaceutical proteins of many kinds, antigenic DNA sequences for use in diagnosis, and in synthetic and recombinant vaccine manufacture. In the agricultural field, patents for plant gene sequences and genetically manipulated plants are also being routinely obtained. In many such patents, extremely broad claims are being granted in response to strong commercial pressures to secure dominance over selected areas of the technology. These legal prizes awarded to those 'first past the post' are highly pre-emptive and have the effect that others in second or third place are forced to seek licences or leave the field altogether.

The response of the patent law to this situation will be expressed largely through the application of the test of inventiveness to these all-embracing

claims. It would therefore be highly desirable to be able to derive a common pattern from the cases discussed above. In pursuing such an ambition, a British commentator must bear in mind the cautionary words of the UK Court of Appeal in the Johns-Manville case (*supra*):

> I have endeavoured to refrain from coining a definition of obviousness which counsel may be tempted to cite in subsequent cases relating to different types of claims. Patent law can too easily be bedevilled by linguistics, and the citation of a plethora of cases about other inventions of different kinds . . .
> I doubt whether there is any verbal formula which is appropriate to all classes of claims.

Nevertheless, the following suggestion has been made (Crespi, 1991):

> Even though the patent application is the first to show the preparation of a DNA sequence coding for a particular known peptide or of a hybridoma which produces monoclonal antibodies to a particular known antigen, there will be a presumption of obviousness if it can be shown that, at the relevant date,
> (a) to apply the known methods of recombinant DNA or hybridoma technology to derive the particular product was obviously desirable, and
> (b) the methods available to the skilled person were considered likely to succeed, and
> (c) the available methods did in fact succeed without the need for significant modification.
> Where these three conditions are met the presumption of obviousness can of course be displaced in any particular case involving special factors. The only firm general conclusion must therefore be that no such test formula will ever avoid the need, case by case, for advice from patent lawyers.

**Patents for higher organisms (plants and animals)**

As outlined previously (Crespi, 1985, 1989), the patentability of living organisms, from bacteria to plants to animals, has shown a linear development over the past decade. This may be summarized as follows. After a period of some uncertainty and (in the USA) strong opposition, micro-organism patents are now routinely granted by the US, European and Japanese Patent Offices. The US Supreme Court had previously held that the 'discovery of some of the handiwork of Nature' was unpatentable, but in the celebrated Chakrabarty case in 1980, the US Supreme Court decided that a micro-organism was not precluded from patentability solely because it was *alive*. Thus a *Pseudomonas* manipulated to contain more than one plasmid controlling the breakdown of hydrocarbons (therefore allegedly more useful in dispersing oil slicks than the natural organism containing only one such plasmid) was 'a new bacterium with markedly different characteristics from any found in Nature' and hence not Nature's handiwork but that of the inventor. The 'product of Nature' objection therefore failed and the modified

organism was patentable. This decision was influential in most other industrially developed countries and the issue is now settled in law.

Plant patents are also obtainable in the USA, Europe and Japan. The US Plant Patent Act of 1930 is restricted to asexually propagated plants and over 6500 of such plant patents have been granted (mostly for rose and fruit trees). In the Hibberd case (Ex parte Hibberd 1985), following the principle established in the Chakrabarty case, it was decided that normal US 'utility' patents could be granted for other types of plant, for example genetically modified plants.

In Europe, the patent law was originally considered unsuitable for protecting new plant varieties developed by traditional breeding methods. Special national laws of plant breeders' rights (also called plant variety rights) were therefore established in some countries in the 1960s, as well as the International Union for the Protection of New Varieties of Plant (UPOV). To avoid legal confusion, patent law in Europe subsequently excluded plant varieties from patentability, for example in the prototype provision of EPC Article 53(b), which excludes patents for 'plant and animal varieties' and 'essentially biological processes for the production of plants and animals'.

Plant breeders' rights have been highly successful in their own sphere. However, it is now generally recognized that patent law is the better suited to the protection of recombinant methods for producing transgenic plants and the resulting products. Patents of this type, claiming methods and products *per se*, are now granted by the EPO.

Animal breeds produced by traditional methods have no legal system for their protection comparable to plant breeders' rights. Based on the micro-organism and plant patent precedents, in 1987 the US Commissioner of Patents declared that US patents would be granted for 'non-naturally occurring non-human multicellular living organisms including animals'. The first transgenic animal patent was US 4,736,866, issued in 1988 to Harvard University with claims covering the 'onco-mouse', one in which an onco-gene has been introduced to make the animal more susceptible to cancer and therefore more sensitive to testing possible carcinogens. The grant of further US transgenic mouse patents was held up until 1992 when three more issued. After initial reluctance by the EPO to grant the corresponding European patent (and a successful appeal to the Appeal Board), the European patent issued. This is now under formal Opposition by anti-vivisection and animal rights groups.

By those who oppose such patents, certain freedoms for breeders and farmers are said to be threatened by patents on transgenic plants and animals. Under plant variety rights (PVR), breeders previously enjoyed the so-called 'breeder's privilege' or 'research exemption', which gave them the freedom not only to use protected plant varieties in their breeding programmes but also to commercialize the further varieties developed therefrom (often only 'cosmetically' different from the original) without any royalty payment to the owner of the initial variety. The UPOV Convention as revised in 1991 now expands the scope of the breeder's right to include what are termed

'essentially derived' varieties (this term is defined). This revision awaits ratification by Member States.

The *freedom to research* is safeguarded equally under both patent law and PVR law. But the freedom to *commercialize* the resulting products of research depends on whether or not they infringe the patent claims or are 'essentially derived' under PVR law. A strengthened UPOV-type protection would therefore go part of the way towards the strong protection given by patents. Neither system is a threat to the free use of existing germ-plasm, since these rights can in no sense monopolize known material as such. Again, until the UPOV revision is taken up in national laws, farmers legitimately sowing seed of a protected variety are legally free to save part of the seed from the first crop of plants for sowing on their own farms to produce a second and subsequent crops (the 'farmer's privilege'). Recognizing that the current scale of use of farm-saved seed thus deprives the breeder of significant royalty income, the strengthened right under the 1991 version of UPOV would now make this subject to authorization of the breeder. However, contracting states can 're-introduce' this freedom under their national legislation 'within reasonable limits and subject to the safeguarding of the legitimate interests of the breeder'.

Now that the 1991 UPOV no longer prohibits the availability of both types of legal right (patent and PVR), plant breeders who are themselves using the techniques of biotechnology alongside traditional breeding methods can obtain both types of protection as appropriate.

## Gene patents and current issues

The tissue plasminogen activator and erythropoietin patents discussed above are examples of gene patents which have had to stand the test of litigation. In the course of this ordeal, the principle of granting gene patents was never in question before the court. But outside the legal forum, the concept of such patents has been seen as a controversial issue. It may be asked whether the biological function of DNA is so fundamentally different from that of other bioactive substances (e.g. antibiotics) that different legal considerations should apply when considering the question of legal rights. Patent law itself cannot make such a distinction. The intimate connection between DNA and life processes is not a legal reason for excluding it from patent protection or even for treating it according to criteria different from those that apply to other large molecules, such as the products of synthetic polymer chemistry.

Genes are a special example of the broad class of naturally occurring materials which in appropriate circumstances can be patented, as discussed above. Where it is necessary to isolate and characterize a natural product and to devise a process for producing it in quantity before it can be utilized by human beings for any practical purpose, the patent law offers scope for protection. Mere pre-existence of the substance, in admixture with vast quantities of other materials, is insufficient to contradict this view. This is the declared position of the EPO quoted above and of the European Commission (see later). It is also the implicit view of the US patent authorities in relation,

for example, to naturally occurring micro-organisms which can be patented as 'biologically pure' cultures. So the feature of isolation or purification of the natural material comes into play to allow such materials to be patented, not in the form in which they exist in their natural condition but in the form resulting from human intervention.

A highly instructive example of a gene patent is US patent 4,885,25112 (Eli Lilly Co.). This is based on the isolation of a gene from an antibiotic-producing micro-organism and the determination of its nucleotide sequence. The gene codes for an enzyme which catalyses the cyclization of a certain tripeptide into the iso-penicillin N cyclic structure in the biosynthesis of pencillin and cephalosporin antibiotics by the *Pencillium* and *Cephalosporium* moulds. The isolation of the gene and its incorporation into an expression vector is said to offer the prospect of driving the natural fermentation process with greater efficiency. Also, it may be used to adapt the natural process so as to convert other tripeptides into products which are different from the natural antibiotics, leading to further antibiotic diversity. The patent describes the construction of plasmids containing the gene and their insertion into a wide range of host micro-organisms. One of the claims is: 'An isolated DNA compound that encodes isopenicillin N synthetase from *Cephalosporium*'. It will be noted that by specifying the term 'isolated', this claim does not cover the gene in its natural environment.

Another claim of the patent specifies the full sequence of 339 codons in the coding strand of the gene, and yet another claim is directed to the enzyme expression product in terms of its amino acid sequence.

## INTERMEDIATES AND cDNA FRAGMENTS

The patentability of gene/enzyme patents of the type exemplified in the last section is clear-cut. One of the patentability criteria of US law is that the invention must be 'useful' and it is evident that the isopenicillin N synthetase invention qualifies in this respect. Patent utility is not to be equated with commerical utility. The patent must identify the utility and describe how the skilled worker is to use the invention, but the Patent Office is not entitled to demand proof of the commercial feasibility of the claimed process or product. A patent may be perfectly valid on the grounds of novelty, inventiveness and utility, even though the invention fails to meet commercial criteria.

## UTILITY IN US LAW

A substantial US case law exists on the subject of utility in relation to intermediates useful in synthetic chemistry, especially in the field of steroids (Maebius, 1992; Daus, 1992). The US Supreme Court has stated that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion' (Brenner v Manson 1966). The court held that chemical compounds are not 'useful' simply because they are used in research. Patent utility arises 'where specific benefit exists in currently available form'. Consequently, certain steroid intermediates were held unpat-

entable in the absence of evidence that the end-products into which they could be converted were themselves biologically active and useful.

The Brenner v Manson ruling must surely be one of the factors relevant to the current debate over attempts to patent DNA sequences, the biological function of which is as yet unknown. This debate has arisen over the attempt first by the US National Institutes of Health (NIH) and then by the UK Medical Research Council (MRC) to patent 'expressed sequence tags' (ESTs), fragments of DNA isolated from cDNA libraries prepared from human brain. This debate has been unusual in many respects. First, the NIH patent application filed in the US Patent Office (and later in other countries) has been the subject of commendable open disclosure by NIH and extensive comment by individual eminent scientists and both public and private sector organizations. The second remarkable feature of the situation is that the scientists have dominated the controversy leaving the patent attorneys to concentrate on the legal question whether these sequences are patentable. Few are yet prepared to pronounce dogmatically upon this latter point, this being yet one more instance of the tendency of biotechnology to put the patent lawyers under strain to make predictions. Various potential utilities are asserted for these sequences: use for isolation of full coding regions of the corresponding genes, forensic uses, and use for gene mapping, tissue typing and antisense technology. One independent commentator has assessed this catalogue of uses as 'more of an invitation to experiment than concrete utilities' and has described the first quoted use as a 'use of compounds as tools for the researcher in search of valuable end-products' (Maebius, 1992).

The scientists and the biotechnology companies have argued over the merits of allowing patents of this sort and even more strenuously over whether patenting may conflict with the principle of international scientific collaboration in the human genome project. This third aspect of the EST debate is notable in that the applicants for the patents have themselves presented an ambivalent attitude to the question whether or not they are entitled to a patent. Thus they claim primarily to be testing the point of law, coupled with a readiness to abide by a decision from the proper authority, a situation which must be extremely rare if not totally unprecedented in patent history!

The initial rejection of the NIH application(s) by the US Patent Office has been contested by NIH and the issues may have to go to appeal unless, for policy reasons unconnected with patent law, the application is abandoned by NIH. If these sequences eventually turn out to be patentable, none of the parties wishes at this stage to forego the possibility of protection and to lose out to the others by being over-zealous to maintain scientific purity. Precisely how relevant patents on such cDNA fragments will be to eventual attempts to patent the whole genes to which they relate is not immediately clear.

## INDUSTRIAL APPLICABILITY IN EUROPEAN LAW

In the regional law of the European Patent Convention (EPC) and in the corresponding European national laws, there is no requirement for 'utility'.

The counterpart provision is that the invention must be 'susceptible of industrial application' as stated in EPC Article 52(1). A particular group of inventions which are expressly classed as not susceptible to industrial application is set out in Article 52(4). These are 'Methods for the treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body'. This exclusion applies only to *method* claims, the philosophy being that a patent should not impede the activity of medical practitioners. Of course, patents for drugs, devices and other products for use in any of these methods are not excluded from patentability, since there is no philosophical problem involved in legally controlling the manufacturers of such products. There is some EPC case law on inventions refused under the specific Article 52(4), but little or none under the general Article 52(1).

By way of speculation, consider the possible case of a novel and inventive method of *in vitro* fertilization, which is effective for both human and animal propagation. Such a method would not be clearly ruled out by the wording of Article 52(4) above. But it is possible that the human application of the method might be objected to on the ground that it is normally carried out in a hospital or clinic rather than in an industrial context. The animal application would not be open to this criticism. However, bearing in mind the liberality of the European patent system and the rule that all exclusionary provisions must be interpreted as narrowly as possible, it would be unwise to attempt a conclusion on the point.

A good illustration of the rule of interpreting exclusions narrowly is provided by a series of decisions of the EPO Boards of Appeal on the question of diagnostic methods. In one remarkable case (Bruker T385/86), the claim was to a particular 'Method for the non-invasive determination of chemical and/or physical conditions inside a whole intact living animal or human body' using magnetic resonance spectral measurements to determine the pH or temperature of local body areas. The purpose of obtaining this data was clearly in the context of diagnosis and the EPO had therefore rejected the application under Article 52(4). But because the claim did not include the final step of reaching any diagnostic conclusion from the data, the Technical Board of Appeal held that it could not be excluded on this ground. The claimed method was one of data acquisition or processing that could be used in a diagnostic method but did not itself immediately indicate a diagnosis. The fineness of this distinction is clearly very helpful if the claims can be written in this indirect way.

Industrial applicability is in one sense a more focused test for patentability than that of US utility, which need not be industrial. On the other hand, the notion of mere 'susceptibility', that is, capability rather than proven actuality, does seem to open the door to the admission of inventions whose industrial applicability is potential and perhaps entirely speculative. On a more practical note, the EPO insist that an invention be presented wherever possible as a solution of a problem and their Appeal Boards regularly adopt this sort of analysis when deciding on disputes over inventive step. Thus the problem is first identified, the nearest prior art is selected for comparison, the patent

description is examined to see if the invention actually solves the problem, and a conclusion is drawn as to whether inventiveness was necessary to arrive at the solution. It is hard to see how an entirely speculative piece of research, which might or might not eventually lead to something of practical importance, would stand up to this kind of legal analysis. It will be some time before these issues are settled in the official examination of the EST patent applications and others which may already be in the pipeline. In the meantime, the EPO Examiners are no doubt following the public debate with considerable interest.

### Opposition to biotechnology patents

The industries that utilize biotechnology are convinced that intellectual property should be obtainable for the inventions that stem from research and which have commercial potential. Increasingly, this view is shared by biotechnology research workers in universities and other academic research institutions in need of research funding. A serious challenge to this assumption has come from a number of special interest groups concerned variously with matters of ecology, animal welfare and rights, moral issues and the interests of small farmers and the developing countries. Some of these groups have formally opposed specific European patents and demanded their revocation. By many such groups, 'patenting life' is considered unethical in principle. The opposition extends also to possible structural change in the agricultural industry which might stem from biotechnology, and especially from the acquisition in the hands of the larger corporations of monopoly rights on the advances that are being made.

## LEGAL AND MORAL OBJECTIONS

Many of the arguments used by opponents of biotechnology patents are outside the permissible grounds of objection provided in the patent law. The authorities are therefore not empowered to revoke patents on the strength of such arguments. However, one legally permissible ground of objection is that genes are naturally occurring entities and that the methods for transferring them to plants or animals are well known and straightforward. This is a challenge to the inventiveness content of the particular patent at issue: it is an argument that industrial competitors will sometimes use against each other's patents, but so far it has not achieved a high success rate.

Some people claim it to be wrong for a patent to confer on anyone the 'ownership' of living things. This is particularly sensitive as regards animals, which patents are said to reduce to the status of mere objects which can be treated according to the whim of their owner. This emotive view seems to ignore the fact that plants and animals are owned by the farmers who produce them and use them as agricultural commodities. All such owners are bound to respect animal welfare legislation.

## ETHICAL ISSUES

The question which immediately prompts itself is whether the patent law is an appropriate vehicle for ethical ideas and moral judgements. Some would suggest that these issues are more properly in the province of laws dealing with individual and corporate behaviour and not at all the concern of the patent law. The alternative view is that patents are granted by public bodies, which by their nature cannot ignore issues of concern to the population at large, especially those having ethical relevance.

European patent law opens the door to this debate by prohibiting the grant of patents on inventions 'the publication or exploitation of which would be contrary to "ordre public" or morality' [EPC Article 53(a)]. In addition, as discussed above in connection with industrial applicability under EPC Article 52(4), certain methods of treatment and of diagnosis are also prohibited from patentability. This latter exclusion is primarily based on the view that these methods lack industrial character, but perhaps it also contains an undercurrent of the idea that preventing medical operations from taking place is unethical. National patent laws in Europe also contain these exclusions. Since these provisions exist, it must be expected that on occasion patent offices will have to make judgements on moral questions.

According to the discussion of Article 53 (a) in the EPO Guidelines (EPO, 1992), it is stated that 'This provision is likely to be invoked only in rare and extreme cases. A fair test to apply is to consider whether it is probable that the public in general would regard the invention as so abhorrent that the grant of patent rights would be inconceivable'. The only example given in the guideline is the rather unrealistic one of a letter-bomb. It is not easy to suggest a range of more likely examples.

## THE ANIMAL PATENT ISSUE

In the onco-mouse case, the EPO allowed the claim to the transgenic mammal but reserved an open position on the generality of transgenic animal patents in view of ethical issues. The EPO had originally stated that it was not equipped to deal with the morality of animal welfare. Nevertheless, the Appeal Board instructed the EPO to consider the question and suggested a line of approach for the task.The EPO were to balance the potential of the invention for human good against the possible risk of harm to the environment and the undoubted harm to the test animal. The EPO then decided that the benefit to cancer research outweighed the other factors and granted the patent. As this patent has been formally opposed on ethical grounds, the argument continues. In another pending application involving a transgenic mouse in the screening of substances as hair-growth stimulants, the EPO took the view that the benefit did not justify the use of such an animal model.

## PATENTING HUMAN MATERIAL

The patenting of human cellular material has been accepted for many years by the authorities as a natural extension of the patentability of lower life-forms such as bacteria and yeasts. Indeed, there are precedents for the patenting of cell lines derived from human tissue which are useful in research and in industrial processes. Although of human origin, these cells remain as individual cells incapable of being organized into any higher level of life-form. The patenting of biological material of this kind should remain non-controversial.

At a lower level still, genetic material – DNA sequences – isolated from human sources and biochemically modified for transfer to industrially usable simpler organisms, are the basis of recombinant DNA patents granted in many countries. These DNA sequences code for the production of therapeutically important proteins useful in human medicine, and there is no doubt that such inventions are morally acceptable and desirable.

However, one European patent for a DNA sequence derived from human source material has been the subject of a formal Opposition from a political party. The Green Party have opposed European patent 112,149 granted to the Howard Florey Institute of Experimental Physiology and Medicine for a gene sequence coding for human relaxin, a hormone involved in reproduction. The gene was isolated from ovarian tissue removed in the treatment of an ectopic pregnancy. One of the arguments on which this Opposition is based is that it is 'an offence against morals to exploit the pregnancy condition of a woman by removing tissue from her ovary and using it as the basis of a profit-oriented technical process'. The Opposers seem to have overlooked the fact that the termination of an ectopic pregnancy is frequently essential to preserve the life of the mother and is morally permissible in both Judaistic and Christian moral thought.

But at the higher level of human cellular organization there is at least a theoretical question whether any limit should be put upon the kinds of biological material that can be patented. It is perhaps far-fetched to contemplate the possibility of reconstructing human organs by means of biotechnology, although the genetic modification of animal organs for use in human spare-part surgery is already in prospect. Whether a human being, as such, could be patented is a related question which keeps haunting this debate, even though one can scarcely imagine the circumstances in which it could become a real and practical question. Legislators have not hitherto dreamed of the necessity to discountenance such a bizarre notion. Nowadays, humans cannot be objects of property rights and it is arguable that provisions such as EPC Article 53(a) would be effective to dispose of any attempt to pursue this absurdity. Similarly, as humans are not 'products' in an industrial sense, it could be held that inventions to 'produce' them are not susceptible of industrial application and are therefore ruled out by EPC Article 52(1).

DIFFICULTIES IN APPLYING THE MORAL TEST

The whole question of morality is beset with difficulty. Is the morality in question to be based on institutional religious belief in the predominantly Judaeo-Christian culture of Western Europe, or is it the prevailing morality of a secular modern society? Whatever moral backcloth is relevant, there are deep-rooted divisions of public opinion on major issues such as pacifism, abortion, human *in vitro* fertilization and animal rights. To intervene in these matters involves a burden which patent officials are not trained to bear.

It ought to be possible to side-step this problem by appeal to the principle, mentioned above in connection with diagnostic methods, that all exclusionary provisions should be narrowly construed. Applying this principle to the morality issue would suggest that a patent should be refused on this ground only where there is an overwhelming consensus that a particular invention is immoral (the EPO has in fact expressed this view in a more recent case). Thus the objection should not be invoked by patent authorities merely on the basis that some section of society condemns the activity as immoral. This would be consistent with the original EPO guideline, but it does not seem to have been invoked by the Appeal Board in the Harvard case. The test devised by the Appeal Board, which is evidently to be used as a standard for transgenic animal cases, is one which is highly subjective. It will often be very difficult if not impossible for patent officials to assess the benefit against the harm of particular inventions, since these may only be properly revealed in the longer term and not at the early stage at which patent applications come before the authorities for adjudication. The ethical questions discussed above have recently assumed importance in connection with the proposals of the European Commission concerning the legal protection of biotechnological inventions. This topic was also discussed in Crespi (1989), but deserves recapitulating in the light of subsequent events in the political arena.

## The proposed EC directive

In November 1988, the European Commission proposed a Directive on the legal protection of biotechnological inventions from the Council of Ministers to EC Member States. The Directive sought to secure harmony in the expanding community between national laws and the EPC, uniform interpretation in the courts, and to upgrade national patent laws in Europe to US and Japanese standards as far as possible without clashing with the EPC. The draft Directive was discussed sufficiently in Crespi (1989) and therefore only the recently proposed changes to it need be outlined.

Article 2 provides that no invention is to be refused patent protection for the *sole* reason that biological material is involved. This includes any matter capable of being replicated through a biological system and it therefore covers living matter, viruses, genes and other types of DNA and RNA. This principle has been accepted for many years in the major industrial countries. Article 3 provides specifically for the patentability of plants and animals and parts of these except for 'plant and animal varieties'.

At the instigation of the European Parliament, Article 2(3) of the current Draft excludes from the above any invention 'the publication or exploitation of which would be contrary to public policy or morality'. As indicated above, the EPC and laws of most Member States already contain a similar exclusion [e.g. in EPC Article 53(a)]. However, Article 2(3) goes on to specify particular examples which for this reason cannot be patented. These include 'the human body or parts of the human body *per se*' and processes for modifying the genetic constitution of humans and animals which, in the case of humans, are 'for a non-therapeutic purpose contrary to the dignity of man' and, in the case of animals, 'are likely to inflict suffering or physical handicap upon them without any benefit to man or animals'.

As far as parts of the human body are concerned, it is perfectly permissible to patent artificial hip joints and other prostheses. But the notion of patenting real arms and limbs seems so far removed from reality that one wonders how the European Parliament came on to this track. It is to be hoped that 'parts' of the body cannot be interpreted to extend down as far as cell lines and sub-cellular particles, including genetic material, but the explanations given by the Commission in the accompanying commentary on this exclusion do not altogether rule out such an interpretation.

Natural products which have biological utility can qualify for patent protection in certain circumstances (usually as the purified material). Article 7 of the Directive confirms that patents for these products should not be ruled out in principle as mere 'discoveries'. Thus the presence of a product as part of a pre-existing material is not *alone* a sufficient ground for refusing a patent for it.

Article 10 confirms that a patent on a biological material (or a process for producing it) covers the first and all subsequent generations of material obtained by multiplication or propagation provided the crucial characteristics of the original are retained. Patent rights in a product normally become exhausted when the product is marketed by the patent owner or a licensee. However, for a product which can be multiplied biologically, the purchaser can obviously propagate the purchased product for the purpose implied in the sale, but is not legally free to multiply it further for use as propagation material. The European Parliament called for an important exception to this rule by the demand for a 'farmer's privilege' (see above). Article 13 now gives freedom to farmers to re-sow seed saved from the first crop and freedom to breed from the patented animal for renewal of farm stock.

Article 14 covers the situation in which a third party has bred a new plant variety from a patented transgenic plant and has obtained a plant breeder's right for it. If it is deemed 'in the public interest', a compulsory licence to the third party must be granted from the owner of the plant patent 'upon payment of an appropriate royalty'. Articles 13 and 14 are objected to by the agrobiotechnology industry because they detract from the patent right in an unprecedented way.

The final form of the Directive has yet to be determined. From the aspect of intellectual property, the Commission's original proposals were rather modest and fully consistent with what is already the law in major industrial

European countries. As far as agricultural biotechnology is concerned, the combined effect of the compulsory licence and farmer's privilege proposals will be the reverse of what was intended by the Commission's original initiative. Consequently, this industry must seriously question whether a Directive of the kind now envisaged will help or hinder it in the difficult markets for agriculture that are likely to prevail for some time to come.

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