Commercial Implications of In re Bell

A Landmark Decision on
Patenting DNA in the United States

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Introduction

President Clinton has promised the American public a reduction in health care costs. Although political promises are often nothing more than "hot air," his stated intentions to reduce costs in part by focusing on the "gross" profits of pharmaceutical companies has weakened investor enthusiasm for drug companies. Such is particularly true with respect to companies with the potentially highest profit margins — biotech companies. With potential government restrictions on medical costs looming on the horizon, it is worthwhile examining a recent U.S. decision which is quite favorable to the biotech industry. The *In re Bell* decision recently changed the law regarding the patentability of DNA, and thereby provided a more favorable environment for the protection of biotech intellectual property in the United States. Although it is too early to determine all the commercial ramifications of *Bell*, it might provide a vehicle for circumventing legislative cost controls on biotech drugs.

Commercial and Political Issues

Annual prescription drug revenues in the U.S. are 60 billion dollars. Although this is a high number, and would, at first blush, appear worthy of the attention of any efforts to reduce medical costs, it is dwarfed by the 900 billion dollars in annual U.S. health care costs. Annual profits to U.S. drug companies are 25% of revenues or 15 billion dollars — before taxes. The 15 billion dollars in

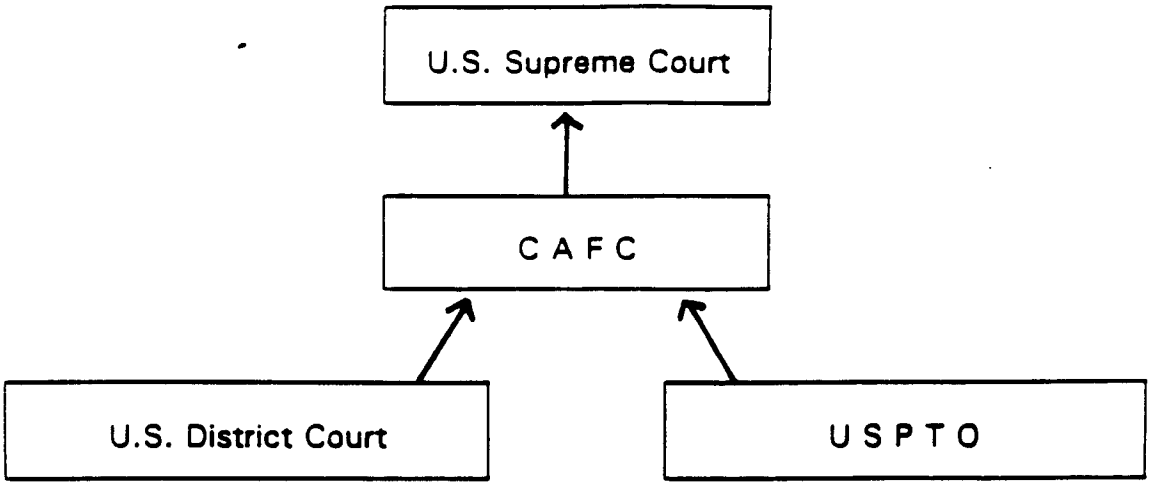
profits represents 1.67% of the 900 billion dollar health care expenditure and less than that if one considers that federal, state and local taxes return about half of the 15 billion dollars to government.

Assuming the above to be true and further assuming that presidents are politically savvy, why would so much attention be focused on reducing the profits of drug companies when the total profits, after taxes, represent less than 1% of the nation's health care costs? First, the elderly are a large and growing segment of the population (12% of the U.S. population is over 65). Second, the elderly are politically well organized and tend to vote in higher percentages than younger people. Third, the elderly spend a disproportionately large percentage on health care (just over 10% of the population account for just over 25% of total drug expenditures). Lastly, health insurance for the elderly in the U.S. (*i.e.*, Medicare) does not reimburse the elderly for much of what they spend on prescription drugs. Thus, when the President (or his wife Hillary who he has appointed head of the health care reform task force) indicates action will be taken to reduce the profits of drug companies, it is viewed by the elderly (many of whom are on fixed incomes) as potentially important to their finances. In that people of all ages tend to "vote their pocketbook," the President's position gets votes regardless of whether it would have any significant impact on overall health care costs.

Congress would need to pass any law the President might propose on limiting the profits of drug companies. However, Congress is subject to the same political realities as the President. Thus they might well support such legislation regardless of the underlying economic realities, *i.e.*, pass legislation to limit the profits of drug companies and appease the elderly even though such would do almost nothing toward reducing actual health care costs. Such being the case regarding the administrative and legislative branches of government, let's examine the judicial branch and how the ***Bell*** decision might make it possible to maintain profits.

U.S. Judicial Branch

Federal judges, unlike presidents and congressmen are appointed for life and as such are not subject to the same political pressures. The Court of Appeals for the Federal Circuit (CAFC) hears appeals from all of the U.S. District Courts (trial courts) on patent law issues, as well as appeals from the U.S. Patent and Trademark Office (USPTO). In that the U.S. Supreme Courts rarely hears patent cases, the CAFC is generally the final word on interpreting patent law in the United States.

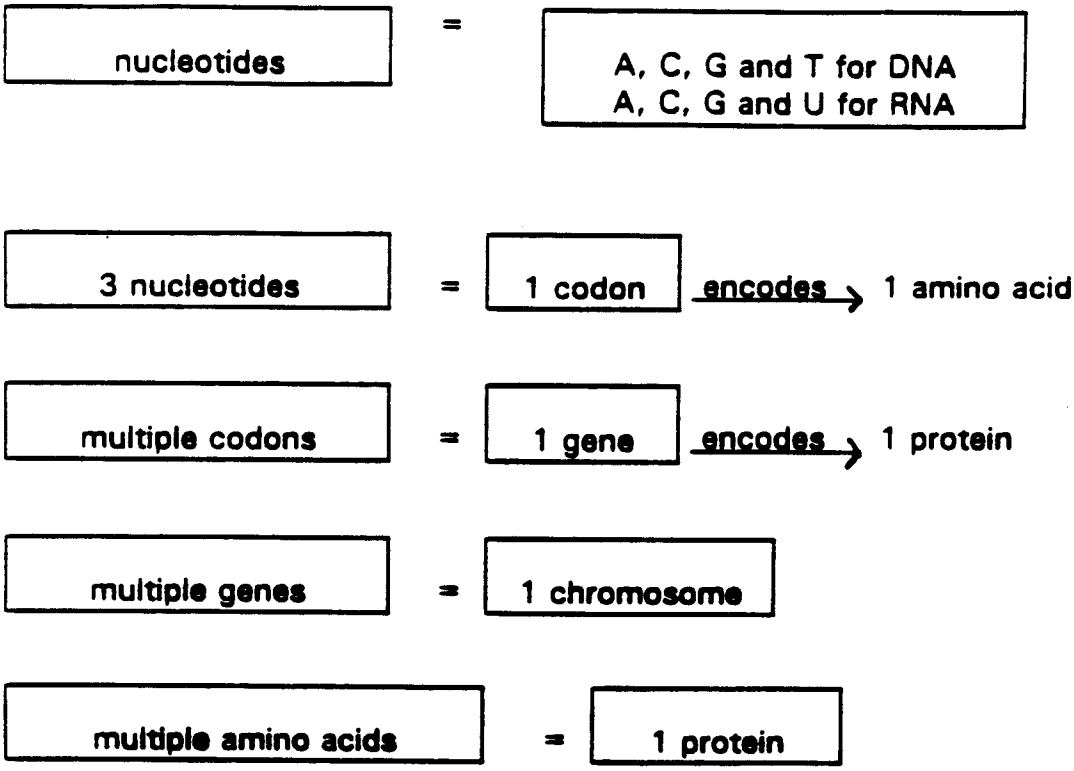


On April 20, 1993, the CAFC issued a decision, *In re Bell*, which is of significant importance to the biotech industry. The *Bell* decision has clarified the standard of patentability of genetic material, such as DNA, which is used to produce proteins. More specifically, under *Bell*, a company can obtain patent protection on the genetic material needed to economically produce a protein. The raw proteins produced might not be considered a drug in that the proteins must be formulated with large amounts of excipient materials to produce the pharmaceutical drugs. It is these drugs which are sold and generate hundreds of millions in revenues. A company producing only the raw protein for sale to a drug company for formulation might obtain a profit not restricted by legislation limiting the profits of drug sales. To appreciate the significance of *Bell* and how it might provide a vehicle for obtaining large profits even in the face of governmental price controls, one must understand the relationship between DNA and proteins.

Technical Background

In living cells, proteins are produced by a process generally referred to as expression. To express a protein, a sequence of nucleotides which make up a portion of the cell's DNA is "transcribed" to produce a corresponding new sequence of nucleotides called mRNA. The mRNA sequence is "translated" to produce (*i.e.*, express) an amino acid sequence, *i.e.*, a protein. Thus, the nucleotide sequence of the DNA provides the basic information needed to produce the correct corresponding mRNA, and thus, the correct amino acid sequence in the protein.

All DNA is made up of a sequence of four different nucleotides: Adenine, Cytosine, Guanine and Thymine, referred to by the letters A, C, G and T. The information stored in the sequence of nucleotides is "read" by the cell in groups of three nucleotides called codons. A set of codons needed to produce a given protein is referred to as a gene. Each chromosome includes thousands of genes and a human cell includes 23 pairs or 46 chromosomes.



A given codon (or group of three nucleotides) will always be read by a cell to give the same amino acid. This correspondence between a codon and an amino acid is the genetic code. There are four different nucleotides which can be linked together in any given sequence of three, so there are 4x4x4=64 different possible codons. However, there are only 20 different naturally-occurring amino acids. This differential between the codons needed (*i.e.*, 20) to obtain all the natural amino acids

and the number of possible codons (*i.e.*, 64) is the basis for the degeneracy of the genetic code — *i.e.*, although a given codon always produces the same amino acid, an amino acid can be produced by (encoded by) more than one possible codon.

GENETIC CODE

given codon = same amino acid

DEGENERACY OF THE GENETIC CODE

given amino acid = encoded by several different codons

Accordingly, if one knows the nucleotide sequence of a given codon, one will know, for a certainty (at least on paper), the amino acid it will produce. However, if one knows the amino acid, one can only speculate as to which of several different codons it might have been produced by. Understanding this principle is essential to understanding the basis of the *In re Bell* decision.

To understand possible extensions of *Bell*, it is also important to note several facts. First, proteins are often known before there is a discovery of the DNA which encodes the protein. Second, the protein might be unpatentable or previously patented by a competitor. Third, proteins are highly active biological compounds critical to the treatment of patients with certain diseases. Fourth, proteins are combined with large amounts of excipient materials to produce the commercial drug formulations sold. Lastly, pure proteins are, pound for pound, among the most valuable substances on the planet. In that many proteins are difficult to produce synthetically, but relatively easy to produce by the expression of DNA, it can be understood that obtaining patent protection on DNA which efficiently produces large amounts of protein could be valuable. Pure protein could be produced by company ABC with a patent on the genetic material for efficiently producing that protein in an economically viable host, *e.g.*, yeast. Company ABC might sell the protein, at a significant profit, to company XYZ (holding the NDA, *i.e.*, government approval to sell the drug) who formulates the protein into a drug which might be sold with

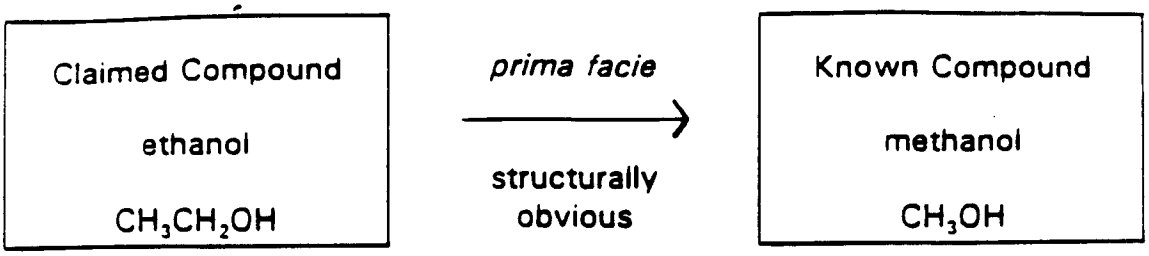
governmental pricing/profit restrictions. The *Bell* decision protects the intellectual property and profits of company ABC.

The *In re Bell* Decision

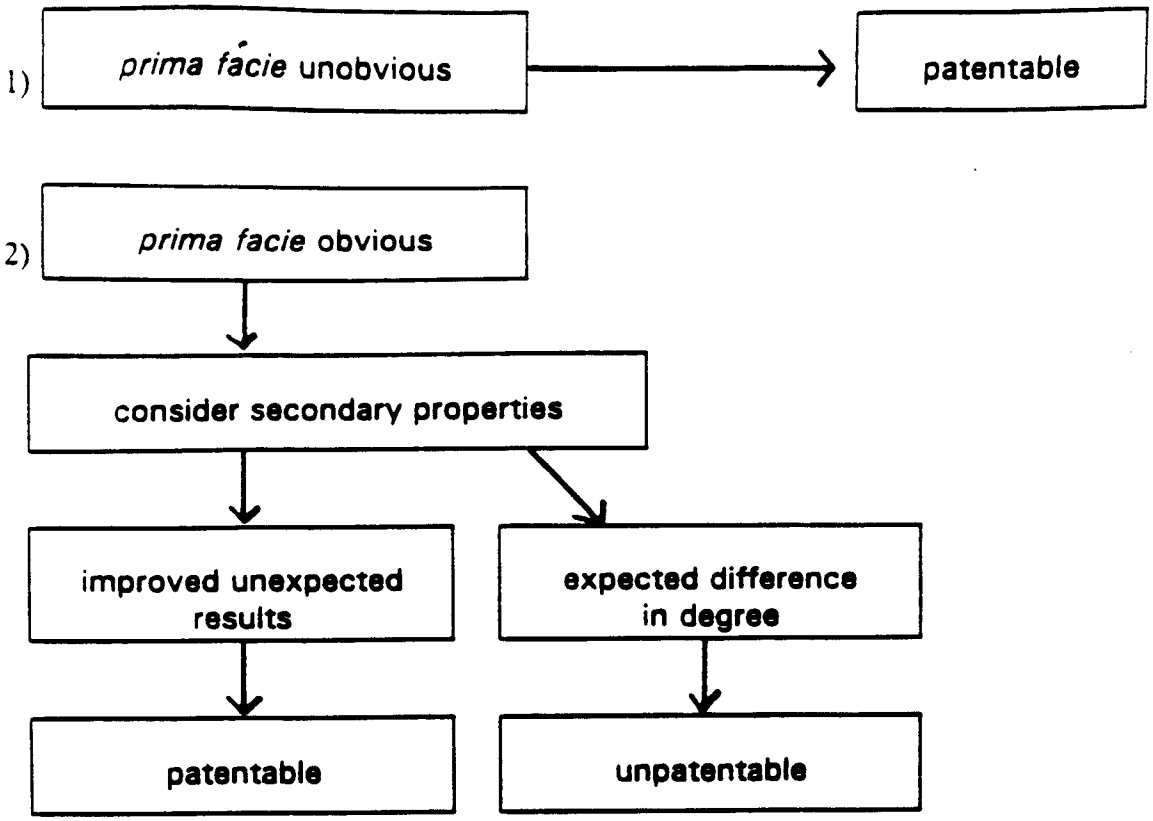
The *Bell et al.* inventors claimed the nucleotide sequences (DNA and RNA) which coded for the production of a particular protein, *i.e.*, insulin-like growth factor (IGF), which plays a role in the mediation of somatic cell growth following the administration of growth hormones. *Bell et al.*'s claims to the nucleotide sequences were rejected by the USPTO as being obvious over two references which (1) disclosed the amino acid sequence of IGF, and (2) taught general methodology for isolating a gene for which at least a short amino acid sequence of the encoded protein is known. The *In re Bell* decision of the CAFC reversed the USPTO, thereby holding the claimed nucleotide sequences unobvious and patentable over the references cited by the USPTO.

The essence of the USPTO rejection was that it would be obvious to use the general methodology disclosed in the prior art in view of the known amino acid sequence of IGF to obtain the claimed nucleotide sequence which encoded IGF. The rejection was maintained by the USPTO "despite the lack of conventional indicia of obviousness, *e.g.*, structural similarity between the DNA which codes for IGF-I and the amino acid sequence of the polypeptide which constitues [sic] IGF-I." The USPTO reasoned that "although a protein and its DNA are not structurally similar, they are correspondently linked via the genetic code."

The "conventional indicia of obviousness" referred to by the USPTO have been established by decades of decisions related to chemical (non-DNA) inventions. Simplifying, these cases hold that the obviousness of a chemical compound is judged on two levels (1) structural similarities and (2) characteristics and properties. An initial determination is made by the USPTO as to whether a claimed compound is, on its face (*prima facie*), structurally obvious in view of known compounds. A claimed compound is generally held *prima facie* structurally obvious over a known homolog, analog or isomer of the claimed compound. For example, ethanol would generally be held *prima facie* obvious in view of methanol.



If *prima facie* **unobviousness** is shown, the claimed compound is **patentable.** For example, ethanol would probably be seen as *prima facie* unobvious over acetic acid CH_3COOH because of the difference between the **-OH** functional group present on an alcohol, such as ethanol, and the **-COOH** functional group present on a carboxylic acid, such as acetic acid. If *prima facie* structural obviousness is found secondary, considerations must be determined, *i.e.*, the USPTO must consider the invention as a whole and consider the properties and characteristics of the claimed compound. For example, ethanol can be "safely" consumed by humans, whereas methanol cannot. This property would not be readily apparent from the structure of the homologous compound (*i.e.*, methanol) and might well be considered "improved, unexpected results" sufficient to overcome any *prima facie* case of structural obviousness, thus rendering ethanol patentable over methanol. However, if neither ethanol or methanol could be consumed by humans and the only difference in properties was that ethanol has a higher boiling point than methanol, such would probably be insufficient to overcome the *prima facie* showing of structural obviousness in that the additional molecular weight of the additional $-CH_2$ group in ethanol would be expected to increase the boiling point.



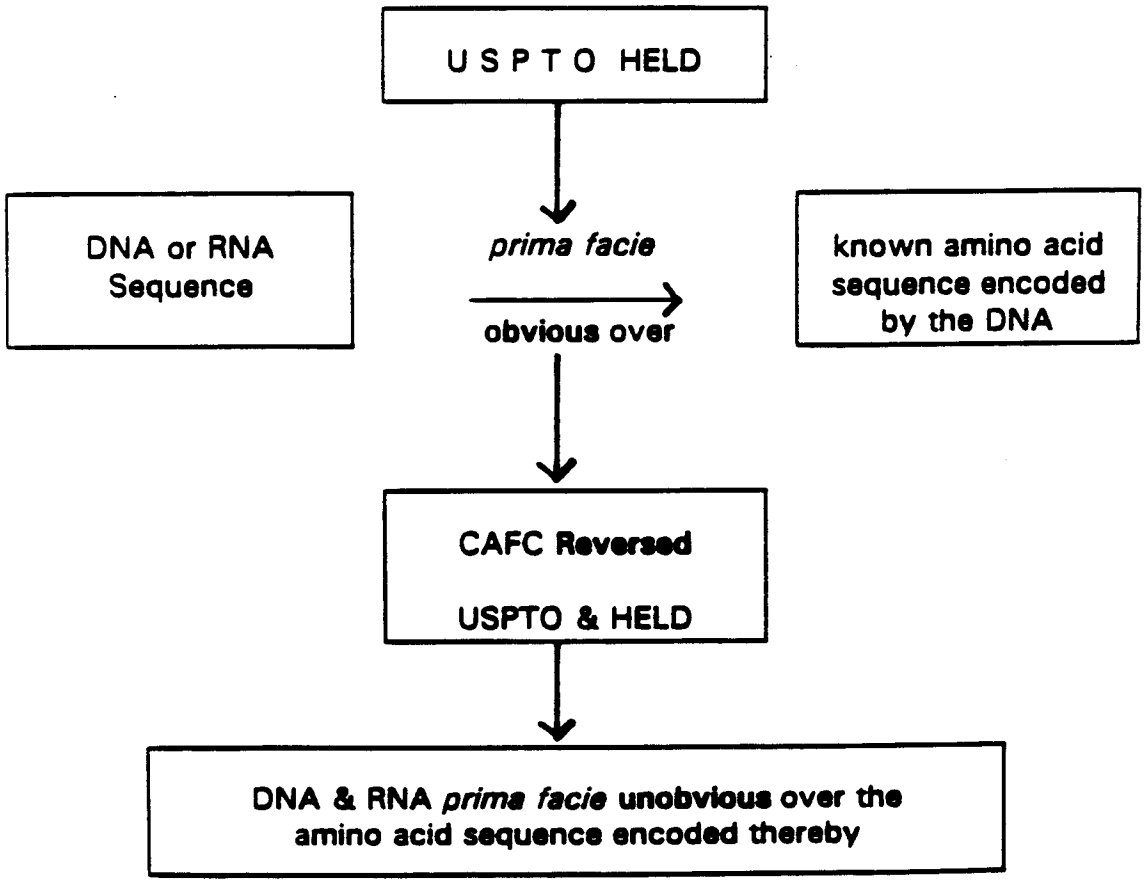
The CAFC recognized that the USPTO was rejecting the nucleotide sequence claimed by ***Bell et al.*** as ***prima facie*** obvious solely over the prior art amino acid sequence disclosed in the prior art. The prior art methodology cited by the USPTO was general in nature and not particularly applicable to finding the DNA of IGF. In reversing the USPTO rejection of DNA encoding IGF as obvious over the known amino acid sequence for IGF, the CAFC referred to the USPTO decision and held:

> Implicit in that conclusion is the proposition that, just as closely related homologs, analogs, and isomers in chemistry may create a prima facie case, the established relationship in the genetic code between a nucleic acid and the protein it encodes also makes a gene prima facie obvious over its correspondent protein. (*citations omitted*)
>
> We do not accept this proposition.

The logic supporting the CAFC's decision mirrors the position which has long been argued by many patent practitioners. Specifically, the CAFC held:

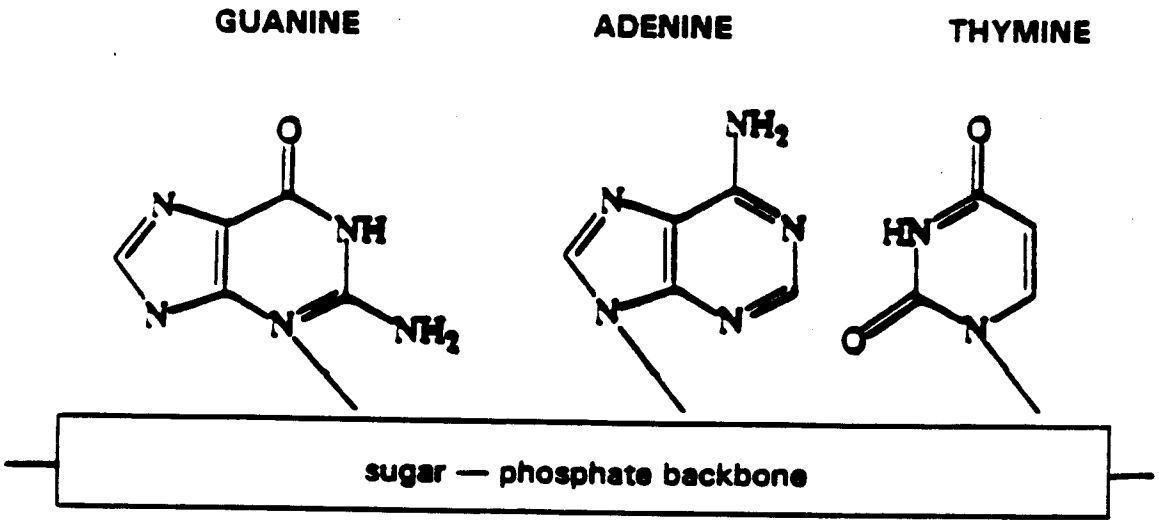
> It may be true that knowing the structure of the protein, one can use the genetic code to hypothesize possible structures for the corresponding gene and that one thus has the potential for obtaining the gene. However, because of the degeneracy of the genetic code, there are a vast number of nucleotide sequences that might code for a specific protein.

Even if *Bell* is given its narrowest possible interpretation, the holding should put an end to rejections of claims to a given nucleic acid sequence (DNA or RNA) over the amino acid sequence it encodes.

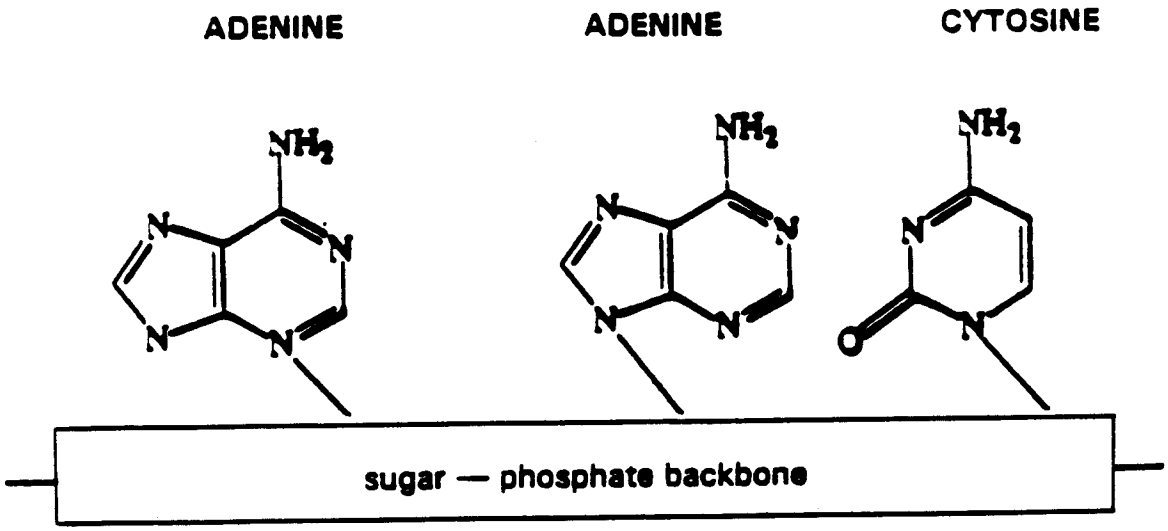


Possible Extension of *In re Bell*

Although the facts of *Bell* did not specifically rule on the rejection of one DNA sequence over another DNA sequence (encoding the same protein), the reasoning behind the decision does allow for such a broad interpretation. One DNA sequence is not a homolog, analog or isomer of another (just as DNA is not a homolog, etc. of the protein it encodes) merely because the two sequences encode the same amino acid sequence. Because any such DNA sequences lack any convention chemical structural relationship, there is, as in *Bell*, no legal basis for rejecting one as *prima facie* structurally obvious over the other. To understand why this is true, one need only examine (on a structural basis) two codons GAT and AAC, each of which encode the same amino acid, *i.e.*, leucine. The structure of the GAT codon is as follows:



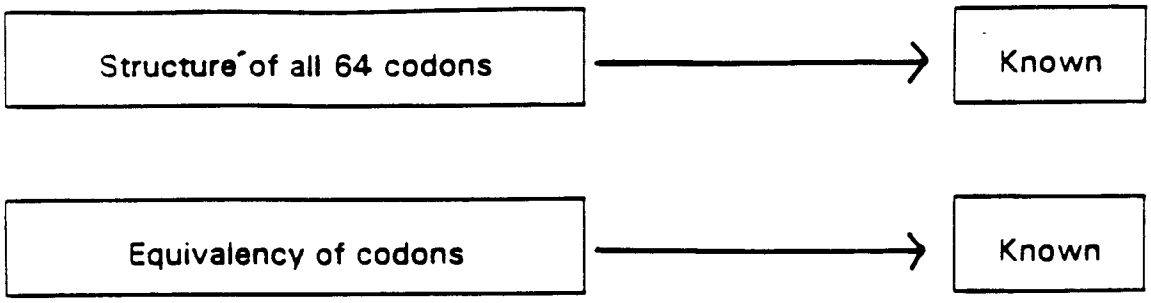
The structure of the AAC codon is as follows:



A comparison of the GAT codon with the AAC codon indicates that one would not be deemed *prima facie* structurally obvious in view of the other using "conventional indicia of obviousness"; they are not homologs, analogs or isomers of each other.

The structural differences between two codons which code for the same amino acid is noted by the above comparison. The structural differences between nucleotide sequences coding for the same protein become greater as the number of different codons increases. The structure of any individual codon is, of course, known. Thus, structural differences between any claimed nucleotide sequence and another nucleotide sequence encoding the same protein might well be held to be *prima facie* obvious in that (1) the structure of all 64 codons is known, and (2) the interchangeability of one codon for another is known, *i.e.*, the degeneracy of the genetic code is well understood.

However, a nucleotide sequence, like all chemical compounds, has properties and characteristics, *i.e.*, secondary considerations which must be analyzed when determining its patentability. The first secondary character of a codon is its ability to express an amino acid. However, this character is not only known but identical for degenerate codons encoding the same amino acid.



However, nucleotide sequences provide something more than an information transfer vehicle. When degenerate codons are substituted in a nucleotide sequence, the new sequence may have different and unpredictable properties which are in addition to the primary information transfer property of the sequence. For example, two nucleotide sequences encoding the same proteins may differ greatly in properties such as polymerase affinity, transcriptional fidelity, endonuclease digestion, etc., and such properties can vary greatly from one cellular host system to another. The physiological features of the intracellular environment where the sequence is expressed are complex. The complexities of that environment are such that one cannot predict many of its effects on different degenerate codons. The inability to predict such is a strong argument in overcoming any case of *prima facie* obviousness. For example, three DNA sequences might, on paper, express the same protein. However, one of these sequences might be digested by endonucleases in a given host cell and express no protein, another might express the protein at low levels, and the third might express the protein at high levels. Such a third sequence might well be judged to have properties sufficient to overcome any case of *prima facie* obviousness over the first or second sequences.

Notwithstanding any *prima facie* case of obviousness, secondary considerations are, as a practical matter, very likely to be present when one is claiming DNA which encodes the same protein as a known DNA sequence. If such secondary considerations (*e.g.*, higher degree of expression) were not present, there would generally be no reason to pursue patent protection. Thus, there is unlikely to be a case decided directly on the issues of whether two DNA sequence encoding the same peptide are *prima facie* structurally obvious in view of each other — secondary considerations will always be present in the properties of the claimed DNA and argued. Hopefully, the USPTO will (1) not await such a decision, (2) rely on *Bell*, and (3) discontinue the practice of rejecting a claimed DNA sequence over a different prior art DNA sequence encoding the same protein.

Conclusion

Despite the lack of real economic reasons for restricting the profits of drug companies, present social and bureaucratic realities make such restrictions politically popular. Drugs sold by biotech companies are often injectable formulations of proteins sold at particularly high profit margins, thus being particularly sensitive to legislative restrictions on profits. The proteins are produced by the expression of genetic material in a microorganism host. Under *Bell* a company can patent the genetic material used to express the protein notwithstanding prior knowledge of the protein. Such protection might allow the producer of the protein to sell it without pricing restrictions to a competitor for formulation into a drug. Thus, *Bell* provides some bases for improving investor enthusiasm as regards biotech companies.

I recognize that legislative restrictions on drug prices are speculative. Further, the ability to circumvent such restrictions under *Bell* is also speculative. However, regardless of whether *Bell* might be used to obtain profits in the face of drug price controls, it is an important decision. It will allow biotech companies to protect their efforts in developing new genetic materials, even when the proteins encoded by that material are known.