Opinion that the human genome should not be used for commercial purposes. Report. Thoughts relating to ethical problems of human genome research.

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Contents

Opinion

The National Consultative Committee of Ethics has often been concerned with ethical problems related to progress in genetic knowledge and its applications.

In 1985, an opinion was published on the problems raised by pre- and perinatal diagnosis.

In 1989, an opinion on the development of identity testing by DNA analysis (DNA fingerprint technology).

In 1990, an opinion on gene therapy.

In 1991, an opinion on the application of genetic testing to individual studies, family studies and population studies. (problems related to DNA "banks", cell "banks" and computerisation).

Additionally a working group is considering eugenics. A session of the forthcoming annual meeting (December 18th 1991) will be devoted to this subject.

Lastly, at the request of the Ministry of Research, a document will shortly be published concerning ethical aspects of the Human Genome project.

A recent event, a request for a patent on a series of human genes, has led the CCNE to publish the present opinion to clarify the application to the human genome of the opinion dated 1990 that the human body should not be used for commercial purposes.

Also, this present opinion will be part of the final report on the theme "ethics and money".

Behind the altruistic objectives of the Human Genome project, its obvious importance for knowledge acquisition and its applications in the field of health, lurk other industrial competition objectives with frightening ethical consequences. Identified genes are not just useful information for the scientific community, but also basic data for future industrial operations via patenting of DNA sequences or monopoly use of the information contained in databanks.

The patent protecting DNA fractions is claimed under conditions which seem to constitute a deviation from normal and ethically justified objectives towards unjustified commercial gain.

This is an exemplary illustration of the difference between discovery and invention.

From the ethical point of view, the problem raised by application of patent rules to the human genome is at the very centre of the principles to which the Committee attach the most fundamental importance.

One of these, on which the Committee has taken a clear position, is the inviolable principle that the human body cannot be put to commercial use.

The other principle to be applied to this case leads to the observation that the sum of information contained in the human genome is the common property of Humanity as a whole; it is an area of knowledge that cannot be appropriated as a monopoly.

It is possible to satisfy this double requirement by insisting on the following position: DNA sequences, whether or not they code for proteins, cannot be patented, they are to be considered as information and deposited in databanks open to the entire scientific community.

International organisations could help in this protection of knowledge against the dangers of monopolisation.

These principles however do not preclude patent protection of products or processes derived from these databanks so long as they are the result of genuine inventiveness and of suitably described applications with proven originality.

Thoughts relating to ethical problems of human genome research

General considerations

The titanic task conceived by various biologists throughout the world is to decode the entire chemical sequence of deoxyribonucleic acid (DNA) contained in the 23 human chromosome pairs. This surely is a titanic endeavour, compared by some to an "Apollo" project for the life sciences. When one considers that the information encoded in the nucleus of our cells is the equivalent of 3.5 billion nucleotide pairs and that the most efficient automatic sequencers can identify a few thousand nucleotide sequences in a few days, the effort and means necessary to achieve such a project can be appreciated, and it will come as no surprise that vast national and international financial support is required.

Advocates of the project see it as, not only an opportunity to meet a real technological challenge (both in instrumentation and applied computerisation), as well as to access important data on human phylogenesis, but even more to locate and identify most human genes. Indeed it should be remembered that, out of the 50 to 100,000 genes thought to be active in humans, only 1,800 have been located on our chromosomes with any degree of precision and very few have been sequenced.

The human genome sequencing project suffers from an ambiguity in the way it was presented to public opinion and the decision makers (the American Congress and the European Community Council) to obtain funding. As such, it can be seen as an *example of the ethical problems* of research particularly focusing on the nature of scientific information given by scientists to the authorities.

Clearly gene sequencing is of major interest in identifying protein structures which are

known to be encoded by the genes and to have a precise function, either to express an hereditary characteristic or to regulate the expression of genes. However this work must be guided by first locating the relatively very small portion of the genome which actually codes for proteins. The study of the possible regulatory functions of the non-coding part of the genome requires experimental work on pure lineages of laboratory animals. Given genetic polymorphism, it is most improbable that knowledge of the base sequence for a single entire human genome could provide any valid information in this area.

This project is frequently justified as a means of locating and identifying genes responsible for human genetic diseases, whether for single-gene diseases or for susceptibility genes for various disorders. Actually, this is a confusion with a project to selectively map regions of the genome responsible for well known genetic diseases, where sequencing is applied only to very limited and specific genes previously located.

Thus systematic sequencing of the human genome is frequently justified as a way to achieve this selective mapping inasmuch as the identification of genes responsible for diseases would be a by-product. However in reality these two projects differ profoundly in their techniques, their research philosophy and in the order of magnitude of the means required.

Indeed it should be pointed out that the intrinsic scientific value of the former project has been increasingly questioned by some biologists, resulting in a significant modification of the priorities. In its most recent version, although it is still called the "Human Genome" project it stresses *sequencing of laboratory organism genomes* , reserving for humans only the development of already existing techniques *of targeted mapping* .

When one analyses the transmission of information by scientists promoting the project to the public, a distinction is apparent between on the one hand the justification presented to create enthusiastic support by the decision makers and on the other, the true motivations of the researchers in their work.

Justification to the public and the decision makers benefited largely from the ambiguities of popularising the notion of a *genetic programme* . Biologists admit that this notion is a metaphor covering, in a single word, all the - actually very little known - ways in which the genome determines the development of an organism and all its morphological and functional characteristics. Interpreted literally, this metaphor suggests the existence of a programme similar to a computer programme, written in the nucleotide base sequence of the DNA. On the basis of this literal interpretation of the genetic programme, the total human genome sequencing programme has been presented as a way to decode the "book of man" leading to an exhaustive knowledge of human nature.

As such, this project has been given a Promethean connotation allowing it to be viewed as a grandiose goal that humanity has set for itself, apparently the only way to convince the authorities to accept the considerable expense required for its completion. Thus the justification for the total sequencing of the human genome is more symbolic than real in regard to the actual scientific value of the project.

In fact, the true motivation of the advocates of this project would appear to be the advancement of fundamental research in molecular biology thanks to the anticipated technological fallout in the areas of laboratory equipment, automatic sequencing and computer processing.

Finally, it is interesting to point out a counter-productive consequence of this over-valued presentation of the project as a sort of "decoding of the book of man".

The literal use of the idea of a genetic programme is consistent with a *picture of mankind in which the notion of the person has been eliminated in favour of that of a programmed machine*.

This idea is not only scientifically unfounded, but also ethically dangerous. Indeed it gives strength to the fantasy that *knowledge of a programme will give man complete mastery over man* . Some sectors of public opinion, particularly in Europe, taking this possibility seriously, far from greeting it with enthusiasm, have reacted with terror. As a result, all things genetic have been looked upon with panic, obviously just as unjustified as the fascination which it was hoped to create.

Therefore, the information which is given out as a result of the project should be carefully monitored to avoid any media amplification which, in a very complex area, could create false hopes or, conversely, false fears.

Budgetary and scientific options

Considering first the budgetary options - and the resultant strategy - in terms of scientific policy, clearly such projects are very costly in personnel and funds. Admittedly, compared to the outlay of funds for military operations of nations, such costs are small in absolute terms. However they weigh significantly on research budgets in relative terms. Thus, in the United States, Congress voted an initial outlay of $200 million. France voted an initial budget of 50 million Francs for 1991, which could rise to 100 million Francs in 1992, without taking into account other funds for activities closely related to the project itself, such as those dedicated to support for the Research Centre for Human Polymorphism, or funds which have also been supplied by some charitable associations (AFM) who have an interest in genetic diseases. The French project will be undertaken in the framework of a public interest group (GIP) a legal and financial entity. Public research organisations should certainly participate in this work very actively (and the salaries of their researchers and technicians should be taken into account if a strict estimate of the total national effort is to be made). Without under-estimating the scientific value of the "genome" project, it should therefore be noted that it represents a financial commitment rendered even heavier by the fact that it can only be credible and efficient if pursued for a reasonable length of time, which could delay development of other biomedical research activities. Our country, as, some others, has put a limit to its ambitions, considering that, in view of present technical feasibility, the exhaustive sequencing of all the genetic information in human chromosomes could only be a very lengthy undertaking.

Two major objectives have been defined:

- to aim to establish a map, as complete as possible, of the active portion of the genome, therefore of the estimated 50 to 100,000 genes (about 5% of the total genetic information). As a first stage, this objective therefore entails at least partial cloning and sequencing of DNA complementary to the messenger RNA from functioning genes.

- to undertake comparative studies of the genome of "model" microbial, animal or vegetable organisms (often called "small genomes") in view of their fundamental or applied interest (infectious pathology, veterinary products, agriculture, etc...).

All the same, as always when initiating heavily funded coordinated state supported programmes, it must be asked if the options are in phase with the opinion of the competent scientific community.

The importance of pre-existing human gene research (locating, sequencing, regulation) should particularly be stressed, while the human genome project is not yet in a productive phase.

A typical example is found in recent work on the fragile X syndrome, the second cause of mental retardation. This work has led, on a fundamental level, to the description of a new

mechanism for the transmission of a harmful gene, and on an applied level, to the development of techniques for diagnosis of afflicted subjects or carriers of a pre-mutation.

Other examples could be chosen among recent work done by French research teams, some of modest size who would hesitate to undertake work on the "genome" project.

One must be careful not to reduce, but rather to increase the means at the disposal of such teams who have already demonstrated their efficiency over several years of research and in a field very close to the long term objectives of the "genome" project.

The two approaches are complementary, one should be careful not to create a disequilibrium to the detriment of apparently modest programmes which have, however, demonstrated their worth.

Ethical problems related to medical applications

One of the major aspects of the project, at the medical level, is the genetic knowledge to be gained concerning modifications which could lead either to genetic diseases (single-gene diseases) or to an increased risk of multifactorial diseases (cancer, psychiatric disorders...).

In this area broad genetic family studies are essential, to gain preliminary information, acquisition of knowledge, and subsequently to make use of the knowledge thus gained. The serious ethical problems arising from these studies have led the CCNE to publish opinions, the conclusions of which should be followed by the research programmes (opinion on the techniques of genetic identification dated December 15th 1989; opinion on genetic testing applications dated June 25th 1991).

All these rules of conduct, in practice, rely on the quality of information provided to the families and, consequently, upon good training of practitioners in this area. However, because applications of fundamental genetic research are so recent, practitioners generally have not received such training during their education. Medical, clinical and biological genetics is not yet a recognised and structured speciality. There is no specialised educational curriculum, no qualifying internship and genetics is not officially a medical speciality.

With increasing demand and the need for good quality of information, to avoid deviation, it is important to take into account this practical aspect, both in the acquisition of knowledge and for the applications, with the same responsibility and means as are applied to fundamental genetic research.

Report

Ethical problems related to the commercial use of the human genome

The ultimate goal of the Human Genome project must be progress in knowledge, health and quality of life.

From the beginning, advocates of the programme have stressed the essential need for rapid and free circulation of information.

In the framework of the Human Genome project, several teams (between 6 and 10 world-wide) have implemented the systematic sequencing (i.e. the sequence of genetic letters which form the genetic code) of fragments of complementary DNA isolated from various "DNA banks".

Complementary DNA, in principle, represents an active gene, so this technique should lead to the study of the useful part of the genome, the part which governs protein synthesis.

Automatic sequencing equipment available today has a very high yield and thousands of complementary DNA fragments have been, or will shortly be, determined.

The accumulation of partial sequences of complementary DNA is therefore a service rendered to the scientific community the object of which is to facilitate and accelerate the acquisition of knowledge of the final products coded for by the corresponding genes.

However, on June 25th 1991, Craig Venter working at the NIH (National Institutes of Health) filed a request for a patent with the US Patent Office concerning 337 "new human genes". In the initial stage, this laboratory determines the sequence of just 250 letters of the complementary DNA, which is more than enough to produce the tools required to isolate the corresponding genes. At this stage, one ignores what the gene is, what it codes for and what it does.

The power of available equipment could therefore lead to patent requests covering thousand of potential human genes: naked genes.

It is necessary to analyse the invention protection process, and that of the dissemination of knowledge and their applications to the genome.

Patents

It should first be noted that patent legislation has evolved (and could evolve in the future) as a function of progress and that there are profound differences between Europe and the United States.

Three criteria are applied to patent protection:

- **novelty**

There is an important difference between Europe and the United States. In Europe the filing date must precede any publication. In the United States, there can be a period of one year between the date of the "invention" (publication) and the filing date.

- **inventiveness**

Inventive activity which makes the work original, is required.

In this respect, it is legitimate to ask if the NIH patent request covering complementary DNA sequences corresponds to this criterion, because the work can be accomplished using available DNA banks and technology which any suitably equipped laboratory is capable of.

- **industrial application**

The request for patent protection must stipulate the potential applications of the invention. There are differences between the United States and Europe on this point: the United States take into account the notion of usefulness of the invention, whereas European patent offices consider the industrial applications.

Also, in the United States, it is possible to confirm the invention by adding new information through the "continuation-in-part" (CIP) principle and thus extend its field of application.

In the case of the NIH requests for patent cover of complementary DNA sequences, their probable function is mentioned as they have selected DNA sequences which could be

expressed (although this is not demonstrated) in brain tissue and thus could be applied to neurological disorders (without further details).

A clear distinction should be drawn between discovery and invention. Article 52 2a of the European Convention on Patents (CBE) states that:

- discoveries are not considered to be inventions

- Inventions are defined "as the act, the process or the circumstance by which knowledge is gained of something unknown or not previously recognised", therefore pre-existent.

- Novelty, inventiveness and concrete application therefore constitute the criteria for distinguishing between discovery and invention.

It can also be recalled that Article 53a of the CBE stipulates that inventions for which publication or application are incompatible with public order and morality cannot receive patent protection.

Patents are also a means of dissemination of knowledge

- at the time of filing the request

Elements that can demonstrate that the "invention" can be reproduced must be put at the disposal of the scientific community: microorganic strain, cells or detailed DNA sequence.

- after a period of 18 months

All documentation must be available in a patent databank.

It is therefore an important source of information.

Data banks

The mass of information generated by Human Genome research and its dissemination can no longer be handled by scientific publications. It can only be processed in databanks by computers.

All research in the framework of the Human Genome project must have access to databanks. The development and possession of such a tool gives researchers a real advantage and can lead to protection of the data to the benefit of a biotechnological industry.

The question of access to the data is thus raised both on the individual and the collective levels. Could those who have invested massively in time and money to produce these tools accept free access for research or industrial competitors. It would not be ethical if unjustified delay in dissemination of knowledge led to delays in potential therapeutic applications.

The question of access to the databanks is directly linked to the question of the "property of knowledge". It is therefore a fundamental problem of research ethics.

This question can be interpreted in the light Article 27 of the Universal Declaration of Human Rights. "Everyone has the right freely to participate in the cultural life of the community, to enjoy the arts and to share in scientific advancement and its benefits", Section 1 supplemented by Section 2 of the same Article, "Everyone has the right to the protection of the moral and material interests resulting from any scientific, literary or artistic production of which he is the author".

Ethical considerations

In the framework of the human genome, how can the principle that the human body cannot be put to commercial use, be reconciled with biological facts and the legal and administrative aspects of patents and the management of databanks.

- Clear criteria cannot be applied to set biological limits: in the human body and its constituents there is a progression from the entire body, to the organs, to the tissues (blood for example), to the cells (spermatozoa for example), to the genes, to cellular messengers (messenger RNA), to the proteins.

Proteins can be marketed and patented with respect to their production (insulin, growth hormone, erythropoietine, interlukins...) and to their applications.

Messengers are labile, but from messengers complementary DNA sequences can be defined, a copy of a gene's DNA information. These DNA copies do not occur naturally, they are artificial chemical substances, they can be used for diagnostic tests, or as a first stage in the production of therapeutically active proteins for example.

- It would be best to set ethical limits by answering the question: what are the threats with respect to ethics?

This approach has already been used by the CCNE concerning the embryo where the definition was not biological but ethical: "a potential human being", in fear, especially, of the production of designer " la carte" human beings.

In the case of the human genome, ethical fears are legitimate, some have already been pointed out in CCNE opinions.

- the fear of biological classification leading to discrimination, exclusion, has already been underlined in the opinion on genetic identity testing using DNA analysis, and in the opinion on genetic tests.

- the fear of the use of genetic knowledge to modify the genome by action on the germ cells, firmly rejected by the opinion on gene therapy.

Other drastic fears are now emerging possibly leading to the appropriation for financial gain of information on the human genome, heritage of humanity, and to the appropriation of knowledge which could become a monopoly reserved for the development of biotechnologies.

These appropriations can be compared to planting a flag on unexplored territory.

Many scientists involved in the sequencing of human genes feel that their activity, supported by public funds or by charitable organisations, is a Service to the community and that complementary DNA sequences, as well as other elements of the genome (microsatellites for example), constitute information which should be freely available, and cannot be appropriated through a patent or through restricted access to a databank.

These new ethical threats call for a new CCNE opinion.