Opinion n° 77

Ethical issues raised by collections of biological material and associated information data : "biobanks", "biolibraries"

Members of the Working Group :

MMES :	N. BAUMANN
	A. CAMBON-THOMSEN
	M. CANTO-SPERBER
	H. GAUMONT-PRAT (moderator)
	B. KRIEGEL
	M. LOIZEAU
	N. QUESTIAUX (moderator)
MM. :	S. BELOUCIF
	G. BREART
	G. ORTH (moderator)

Opinion

Ethical issues raised by collections of biological material and associated information data : "biobanks", "biolibraries"

Collection and processing of human biological samples and of the related information data, raises some major ethical issues, and all the more because of genetic research activities.

Such activities are far from new, but are now undergoing a revolution, because of technical possibilities which have added interest to the collection of physical elements and data on a grand scale, and because genetic research offers new possibilities for any collection. The large banks or biolibraries will be a considerable asset for scientific research on subjects relating to health and the study of populations, to the extent that some countries wish to promote a compilation on a national scale of these collections, which would be viewed as a kind of resource to be exploited.

Concurrently, insofar as it is hardly possible to set out in advance the forms of exploitation which could be used, such collections tend to generate public concern. Although these investigations could well enhance the progress of scientific knowledge and benefit humanity, the Committee cannot see its way to dismissing the fears of public opinion as fantasies and figments of the imagination. When scientific progress needs to be conveyed to the public, the task requires serious efforts in communication. Researchers need to make clear the meaning and the scope of these innovations. It would be regrettable if the reluctance of those who do not wish to participate in collections was due to misunderstanding. However it is not certain that competent dissemination of information to the public will necessarily lead to unanimous approval, since it is no secret that science is not the only social institution to take an interest in the collection of data related to the genetic structure of individuals. Insurance companies, or police investigators, for instance, are particularly interested in the subject. In the circumstances, the object of this Opinion will be to propose some response to a very specific question : what are the conditions which will ensure that collecting and processing of human samples can take place in a climate of trust?

The larger collections could, unless care is taken, become instruments of power. In any event, they have already acquired some value, intellectual value which can be exploited, and which is obviously a potential source of financial gain.

1) A new framework

In order to dispel apprehension, which could easily hamper the development of such activities, a new and coherent framework is required.

CCNE is not seeking to oppose what is being done, nor to call for a single status for all scientific collections although they are of widely differing dimensions and purpose. These activities are presently governed by a whole network of legislation and regulation; they are not left to free enterprise; there is already a structure supported by the rules of unavailability and non-commercialisation of elements sampled from the human body, as reflected in the *Code Civil* and the *Code de la Santé Publique* ; the system for the protection of computerised files under the supervision of the Commission Nationale de l'Informatique et des Libertés and the network of biological resource centres recently created by the Ministry of Research to oversee projects and the establishment of collections.

However, this framework must be modernised in response to three requirements.

It must draw together into a **coherent** system the regulations for the collection of physical elements and those which concern the conservation and computerised processing of the information data, in order to prevent new developments of these activities which could weaken the scope of the rules of unavailability and non-commercialisation of the human body and its components.

It must adapt to the fact that such activities have an impact on others besides the person concerned initially and the practitioner or a given researcher. They may be prolonged over time, for a very long time, be of concern to third parties, come successively under the responsibility of a succession of promoters, or be stored in case of future need by organisations who have been given that specific task. Furthermore, an examination of genetic characteristics may be performed at any time on any collected material; processing of genetic data is not a specific or exceptional event. It must be an integral part of the process.

Finally, it must integrate the fact that not all utilisations can be treated in an identical manner. A person who would be quite willing to cooperate for instance in cancer research, would probably object strongly to the elements and data collected being used to find and identify a criminal. It would be even more unacceptable to ask people to cooperate in a scientific project without protecting them from prohibited discrimination or from the information in question being commandeered by extraneous persons or bodies. Science can only draw benefit from the development of these collections if it provides for security of the data and prevents unauthorised use. This would be the case, for example, if genetic data was used to find and identify a person, even if this were made lawful.

Saying that the status of such activities need harmonising does not mean that a single rigid model of organisation is being recommended nor that it would apply whenever biological material, potentially a vector of genetic information (i.e. containing cells or extracted genetic material directly) is being assembled on any kind of scale, and that to that collection would be added files, possibly computerised, containing the data required for exploitation (donor origins, genealogy, biological and clinical data). The above is a definition of biolibraries.

However, there is a need to decide that the sequence of operations – collection of biological material, storing, processing of information and data, utilisation for a given research project – must be a sequence of responsible events. Responsibility has to be exercised jointly and without interruption. To this end, the present gaps as regards the position of curator or conservator, who would be the centre point between the persons concerned and the various uses for research, must be filled.

The following proposals bear on the setting up of an appropriate system for research in fairly broad terms, medical research for diagnosis and therapy, public health research, population genetics. They do not deal, voluntarily, with problems that might arise because of other utilisations, for civil or criminal purposes or for employment or insurance. The matter is urgent and requires a system specific to utilisation for the health and life sciences, to be defined in such a way as to prohibit access once and for all for other goals.

2) The function of curator or conservator

This renovated system must first of all define **the contents of the function of conservators or curators and their obligations.** This remains the case whether operators are public or private entities, and the activity is always subject to authorisation and specification.

Three categories of obligations must necessarily be included.

- The conservation activity is not tantamount to acquisition or appropriation of the elements collected and the resulting information data. A new service is created which must respond to stringent standards for quality, security, and monitoring. The bank, once it has been authorised to operate, must remain under supervision.
- The curator is at the centre of a network of rights and obligations which must be controlled. Upstream, rights of the persons concerned, and consent, rights of the depositing researcher, archiving arrangements, presumed vocation of the collections; downstream, conditions of access for users to the deposited material and information, protection against prohibited utilisation. This entails within the bank, or close to it, an independent mediating body, with sufficient authority to arbitrate between opposing concerns.
- Finally, the specifications must include provisions regarding the mode of payment for the costs of conservation, which is integrated in a sequence of events based at the outset on an unpaid personal donation.

3) The rights of persons who provide the biological elements in the collections

The person who is at the source of the samples collected has rights which are not a form of ownership of the deposited elements, nor a right to concede those elements, or the associated information data, or the results of research resulting from those elements and data.

That person consents to collection and the ensuing operations. The notion of consent needs to be retained, and the guarantees associated with banking must be defined. Questions must be answered regarding the protection to be given against abuse in the use of elements and information in the collections, and on the possibility of a return of the benefits of research to the person whose consent made it possible.

The creation of banks leads to a **reinforcement of the demands connected to personal consent. The time of deposit in a bank becomes a crucial moment, and that is the time when information and a request for consent must be made available in such a way that it allows the donor to fully understand the complexity of the matter in hand**. It is for that purpose that arrangements must be made to guarantee informed consent on behalf of a child, or an incompetent, or for the protection of the interests of a deceased person. These are essentials which the regulating authorities will need to set out in detail.

There are further difficulties arising out of the permanence of banks, and the repeated or renewed use of their facilities. It could seem at first sight that the best way of solving the problem would be to underline the right of withdrawal from a research project, and the right of access and withdrawal granted by the protection process for computerised files. If that is the approach, the person concerned would have to give renewed consent every time the initial project was in any way modified.
That, however, is where further difficulties arise. The repeat consent procedure requires that the data identifying that person is stored somewhere in the archives. Now, the security obligation specifically requires that the possibility of identifying consenting donors be

suppressed. For someone to claim priority or privilege of access to the benefits of research produces the same predicament.
It is clear that a **respect for guarantees of security and anonymity is the cornerstone of the public's trust and of satisfactory performance by the banks.** This in fact calls for special requirements, which CCNE particularly requests as regards technical investment, and the training of workers processing samples and data. This is the foundation for all the legal assurances which, for example, prohibit any discrimination on the basis of genetic characteristics.

One could therefore assert that some form of proxy, **in the hands of the mediating body**, the creation of which is suggested above, could make it possible for a person to be contacted only if there was a justified need for it. However, anyone could at any time go to the mediating body to find out what has happened to their material and samples. This possibility would be make known in an extended consent form, and the persons concerned would be given the choice of contributing to research in a given domain, or to medical research generally, or to any configuration enabling them to express the limits of their acceptance.

CCNE notes that a question of principle underpins that option, and recommends that the matter be given some thought. These alterations to the notion of individual consent rest on the notion **that the mass of information and connected data have in fact only acquired value for all those participating because they are assembled and cross-matched for a great many people**. They gradually constitute an asset which is detached from the person who has supplied an element of his/her body, the only value of which is the **common use** that progress has made possible.

4) Use for the common good

There is a need to reflect on the notion of solidarity and on the accountability of the national community in a situation where large banks or networks are set up on a population-wide scale.

There are trends, triggered by some spectacular initiatives, in the direction of large scale collecting of elements and data, in particular of a genetic nature, for public health purposes, so that, through cross-matching with other information, they can be interpreted. This may generate a good deal of reticence, particularly when the data is highly prized because it is exhaustive and is the subject of exclusive contracts for use by a private company which could well make a profit by it. One could however claim that privatisation benefiting private interests is not an inescapable corollary of this procedure. If a modern society decides at an appropriate moment that it will make the considerable investment that collection involves, with the full support of its population, it will make progress as regards therapeutic research and public health care. It is not due to chance that a large scale project is taking place in the United Kingdom. For these reasons, it would seem useful to ask a public body to officially investigate the potential outcome underlying such data collection, and to **question French public opinion on the subject on the broadest scale**. In this way, public opinion could become more aware that the contents of banks are an asset which should be pooled in order to make real progress. Better understanding of the issues at stake would facilitate the response that will have to be made to possible reactions and claims by those concerned.

5) The position of researchers

When the collection, storage, and use of the contents of banks lead to interesting results, new relationships emerge between the members of the scientific community themselves, and between the community and those providing the funding. The individual who may, at the outset, have made the whole sequence of events possible, might not remain impassive in the face of this new deal. The public may be influenced by the fact that there is no clear answer to the questions they are likely to ask.

The appearance on the scene of an intermediary, the "bank", tends to spotlight issues which in fact are not new. However, since the legal status and the mode of funding of the curator's activity are not matters which have as yet been settled - and they would need to be - certain pragmatic courses of action or compromise solutions between opposing concerns are becoming obsolete.

Such is the case for relations between researchers and for the financial arrangements governing collection activities.

Relations between researchers and between them and the banks must be structured by some form of contracting procedure. There are two schools of thought regarding the problem. Either the inventor or the initiator of the collection in the bank is given a privileged position insofar as he retains for a considerable time follow-on rights regarding its use, or else the notion of free – or at least very open – access to DNA banks is introduced. To be more precise, access is viewed as open in that it is non-discriminatory, but this does not signify that the service is rendered free of charge. The closer we get to a situation with very large banks created to be a public service to the population as a whole, the more it will become necessary to organise very open access, and it will be increasingly unthinkable to reserve access of valuable DNA collections to the research projects of a certain person or to those of the company that financed it. It is therefore essential that, in cooperation with the scientific community, the authorities take action to define cooperation arrangements and their impact on intellectual property rights.

6) Financial relationships

Here action is all the more necessary because the question of reimbursement of the cost of banking would need to be included in the specifications which would govern both private and public initiatives.

From the outset there is a principle which CCNE would like to see firmly established : samples collected and the associated data, including genetic data, **do not fall within the scope of commercial transactions.** There is no point in reviewing at this stage the fundamental concerns regarding the protection of individuals which make that principle one of the cornerstones of our legal system : the technical developments which the banks bring about are no justification for any encroachment. **The contents of the bank are the fruit of voluntary donation by those concerned. They cannot from one moment to the next become the property of the researcher or the curator.** The latter are in charge of the contents and have a duty to make the best use of them. However, at the end of this sequence of events there comes a moment when, in case of success, creative inventiveness may lead to added value for the results of research in the form of a patent for a test or therapy, for example. It is absolutely necessary to deal with the sui generis situation generated by the collection and conservation services.

There is obviously a need here for legislation. Because of the origins of the biological material, free enterprise is not an option. A procedure must be found to evaluate the cost of the service ; it might well be that a compromise between the various points of view could lead to creativity regarding compensation. For example, if a DNA bank is created by a private company for its own research activities, can it control access, or should there be some kind of legal deposit obligation for part of the material or information for the benefit of open research? Where does it stand in relation to the bank status that CCNE is recommending ? Surely the solution is that it is governed by this status and that suggested organisational models must provide for such a situation.

Replies to these questions imply reflection on the respective involvement in the collections of the private and public sectors in the future. Comparison with other countries shows that there is in fact a consensus for these activities to be controlled, be they public or private. The **traditional instrument in France would be appropriate, i.e. specifications applicable to all, but they should be drafted with a mind to the diversity of legal status of operators.**

Only once such matters have been elucidated will it be possible to pursue a discussion which is still in its infancy: sharing the benefits which result from such research with the participants. There is a need to anticipate public reactions to recognition of new added value to these collections.

7) Sharing the benefits

Three kinds of trends could develop or be amplified. One, common as regards rare or single gene diseases, goes in the direction of positive results being tested or made available on a priority basis to participants. A second and more radical approach would consist in claiming for the person who made a contribution a share of the “royalties” or copyright on the patent. A third approach would be opposition to a collection when it is suspected that the goal is making researchers – or more likely the big commercial companies – more wealthy.

CCNE is voluntarily using in this context the expression “sharing the advantages or the benefit” rather than “sharing the profits”. This leads the Committee to accept that the first claim could, in certain specific cases, give rise to agreement between the promoter of the research and certain groups very personally concerned by specific therapeutic research. However, these would be exceptional cases which should not become the generality. Inversely, the Committee considers that any development in the direction of a return to the person concerned in the form of financial earnings through industrial or intellectual property rights, should be resisted. A tendency towards individual appropriation of biological material and data would be a step backward as regards the guarantees provided by the rules of unavailability and non-marketability of elements of the human body, and would be in contradiction with the principle of use by the community which gives true value to these collections. The moment is ripe for constructing solidarity ; if there must be a sharing out, instruments such as right of access, legal deposition of material (*dépôt légal*) or financial levy on profits with a view to financing projects in the general interest, could be used. Be that as it may, and this brings us back to the issue of the larger national banks, these matters must be addressed in good time, and not left to last minute reactions in the face of expressions of public opinion which are very damaging to scientific research. It is therefore in the best interests of all to consult the public openly on these matters of principle, in particular as regards the possibility of constituting a large bank.

8) A responsibility for the authorities

If CCNE's analysis of the situation is found acceptable, the time has come for a new phase in the progress from ethics to law. It implies a reorganisation and a clarification of the legal framework, in which the sequence of obligations as regards collection, processing, storage, and the use of biological material and related data – including genetic data - must be clearly visible. **To achieve this, an explicit status for biolibraries or biobanks must be instituted, although this does not imply a single exclusive model.**

Supervision of the system must be put in the hands of **a regulating authority.** Its functions would include the traditional task of ensuring the respect of obligations incumbent on banks, both public and private. However, it would also be tasked with working on the conditions governing in practical terms the drafting of consent forms, defining safety and training techniques, and analysing the evaluation for charging the conservation service. Furthermore, it would need to organise consultations and debates about these new instruments for gaining scientific knowledge, and in particular on the advantages and drawbacks of constructing a national resource, or a coordinated network, which comes to the same thing. This would be a way of involving all the intermediate entities who are concerned by the donation of biological material, in particular patient self-help associations who have traditionally displayed a great deal of interest in genetic research. Finally, it should transcribe into a code of good practice the consequences for researchers of this system of rights and duties, which would assist them in their discussions with the international scientific community.

In any event, in this task of reorganisation and policy-making, the key word is: transparency. The sooner citizens are able to understand the challenges these technical developments bring in their wake, the more they will want to continue to cooperate voluntarily to their development in a spirit of respect for ethical principles.

Report

I – Introduction

The Généthon Company referred to CCNE on February 8, 2000, concerning a project for the on-line display of a catalogue of biological samples registered with the Généthon bank, and a draft charter regulating relations between the bank and those persons using its services (contributors, users). This private referral is consistent with a general trend of interrogation on major ethical problems raised by the collection and processing of human biological samples and the information data which it generates, more particularly in relation with the development of genetic research.

CCNE wished to make a full contribution to this international concern by extending the referral to the more general issue of collections and biobanks. Such activities are not new : for a long time, based on many kinds of sampling activities for the purpose of diagnosis, therapy, or research, conservation and classification have been performed to add value to a collection. Such activities are extremely heterogeneous, collecting DNA and the source of DNA, tissues, biopsies, gametes, organs, fluids (blood, cord blood), stem cell lines, embryos, or even fœtuses. Although emphasis is now on collections specifically designed for scientific purposes, such as the Généthon collection, there are also collections of organs and tissues in pathology laboratories, gigantic collections housed in the *Etablissement français du sang* (French Blood Agency) for the sake of traceability, and also collections of samples from vast populations for epidemiological purposes.

Is it not over simple to identify common questions in the name of ethics, about a collection of cells for the purpose of identifying a new gene, or about blood samples systematically collected from blood donors, with no other purpose but archiving ? However, it seems that all these collections, whatever their size or finality, are now affected by a form of revolution.

"Traditional" collecting

Samples and data have always been collected, and this is a continuing activity as part of the normal and ordinary practice of medicine. It is done under the active responsibility of the practitioners and researchers concerned, more often than not with the explicit or tacit agreement of the patients who were at the starting point of what was no more than a commonplace medical procedure. It is financed as part of the medical act by the health insurance system. The data is processed or communicated to other medical teams in a general climate of mutual trust. Patients and their relatives either agree to, or are unaware of these procedures, and are mainly concerned by the hoped for advances in treating their particular condition. The above may also take place in the framework of a fully documented research contract, without this raising any particular problem.

New forms of collecting, in time and in space

A revolution is taking place because the same diseases and the same research no longer dominate the scene. Genetics is playing a lead role following the sequencing of the human genome and the technological developments that it brought about. Any collection of parts of the human body, even if it has been stored for a length of time, could be of interest because it represents a potential source of DNA. There is a shift, in the use of collections, from **symptomatic diagnostic medicine** to **asymptomatic predictive medicine**. The interest aroused by a few very targeted diseases and groups of well identified patients has become more general. Collections are becoming the preferential tool of predictive and collective

medicine, increasingly dependent on the pharmaceutical industry for financing. The importance of these collections for research is recognised ; **they are becoming valuable**. The demands of maintenance are being discovered ; computerisation is opening up a whole new technical field for which training is necessary. Exchange of information and international cooperation are becoming major issues. The circle of those persons concerned is amplified well beyond the scope of the disease which had been the initial reason for sampling, and **these relationships are prolonged in time**.

The change of scale induced by this technical revolution must be emphasised. It is now possible to analyse vast data collections using increasingly efficient techniques. Vast populations can now be the subject of genetic investigation. Not only are the scientific consequences of this evolution considerable, but the incursion of the private sector, as regards not just the means required but also the collection and processing of the samples and data, has become a very important factor. The development of pharmacogenetics in particular reveals the value of examining a very large number of samples. Modern technology, which progresses apace, provides the possibility of establishing profiles of reaction to certain drugs, and therefore to work on their adaptation to the genetic characteristics of patients, however diverse. Here again, research on such characteristics involves analysing very vast collections, much larger than those assembled so far, enriched by information on the health of those persons who contributed to their creation.

A recent study[*] mentions some evaluations done abroad or in France. They give an idea of the space taken up by these collections. More than 280 million samples would appear to be stored in the United States, where hundreds of laboratories are working on human DNA and more than a hundred corporations base their activities on the use of this human material. In France, Evry Génopole had already collected in 2001 more than 46000 samples ; larger quantities are stored in the thirty or so sites under the authority of INSERM and *Assistance Publique-Hopitaux de Paris*. Major work being done in the framework of the European project EUROGENBANK should soon give a more precise evaluation of such developments which have been studied in 147 structures in 6 countries. Some figures are given in the annex regarding some of the more notable projects in other countries.

CCNE sees this as an irreversible evolution, a sign of the change in the paradigm of medicine and medical research. The time has come for vast collections and extensive data compilation derived from components of the human body. Such collections are now far more valuable than anyone would have thought originally. The sector is caught up in a movement which the practitioners or researchers no longer control, on a course for which no one is clearly responsible. Such a situation causes alarm and reticence, which is expressed on several levels:

- **At the individual level.** Individuals enthusiastically accepting to supply a sample so as to facilitate a study for medical purposes, might well object indignantly to that sample being used for some other study which they see as contradicting values to which they subscribe ; for instance studies concerning genetic determinants, sexual behaviour, the relationship between certain psychometric items of information pertaining to genetic markers in a context of ethnic stratification…
- **The commercial level.** A relatively modest collection of rare biological material, clearly identified as to phenotypes, ends up more as a tool for adding value than for true research when the initial project is not clearly identified, associated with a risk of

[*] S. de Montgolfier, unpublished thesis.

transfer or sale on the national or international market, to the detriment of authentic research.

- **The ideological level.** There is the risk of constituting a bank more on the basis of behavioural analyses than on biological data. This over simplification which tries to identify or explain behaviour genetically causes major ethical problems.
- **The national level.** As soon as a bank becomes a powerful tool, there is a non negligible risk of its being used repressively or for discriminatory purposes. Lawmakers must be aware that this is always a possibility, even with the best of intentions. Not only must there be total confidentiality, but it must also be tamper proof against, for example, a change in a political regime.
- **Finally, on the international level.** Using the genetic data of a population or of a country could turn out to be little more than robbery with no or hardly any benefit for the country concerned. Such collections may become an item for economic transaction, and what is ethically difficult to accept on an individual basis, would become even more unacceptable collectively.

As always, ethical deliberation must find a path between necessary technical progress and the respect owed to the human person.

Although in the view of CCNE, further advances in the knowledge we have of human beings and medical progress should not make us apprehensive, there is a need to identify the tensions which such progress initiates.

II. – A first source of tension is generated by the inadequacy of the framework within which such activities will be developing.

Although the attached analysis of the various overlapping judicial systems which apply to the constitution and storage of collection shows that these activities are already largely regulated, there is a need to evolve an entirely renovated system (cf Annex).

Renovation of the system responds to three objectives.

1. Harmonising the various statutes governing biological material and computerised processing

Firstly, there is a need to imagine a coherent framework to cover both the status of the physical elements collected and the rules governing the storing and the computerisation of the data. Genetic science must be reinstated within that system and not singled out for exceptional treatment ; no one can know in advance when a particular avenue of research will have to study genetic characteristics. At present, protective rules are based on various principles: non availability and non marketing of any part of the human body, i.e. physical parts of the human body which are therefore stored in collections as the result of a donation ; protection of sensitive personal data by rights of access and of withdrawal for data files; and finally severe restrictions as regards the scrutiny of genetic characteristics, permitted for authorised uses only.

2. Definition of the status of curator, "librarian", or conservator

There is also a need to define, in the sequence of operations from sampling to discovery and possible exploitation, the status of the custodian of the collection. This action entails a duty of storage, reliability, sanitary safety, monitoring, and rational use of collections which have

acquired a value which was not known at the time of their creation. It furthermore entails the need for an autonomous function which must be delimitated.

On this subject, CCNE entered into an extremely illuminating semantic debate. To designate this new operator, the word "biobank" is frequently used. The origins of the word are blameless. As soon as blood was collected, the word "bloodbank" was used to designate conservation, although there was no mention of the economic conditions regulating this activity. The word was used despite the fact that such collections were the result of donations. The same is true of gamete banks.
The word biobank today seems to allude to some form of deposit of property with a market value. It may appear to be over-emphasising the value of the sample or of the information data. It eclipses the human origin of the samples and the ethical problems which ensue. It would therefore be tempting to coin a word such as "biolibraries" which highlights the notion of archiving. The conservation of books and documents was considered to be for the common good and gave rise to the creation of public libraries constituted by works which were deposited therein. However, although the concept is reassuring when applied to collections, it still does not solve financing problems, nor does it mean that there is no need to consider the purpose of this conservation.

However, a definition which delimits the scope that CCNE wishes to give to this Opinion could be used to support the theory quoted above.

"Biolibraries represent an assembly of biological materials potentially vectors of genetic information (i.e. possessing cells or directly extracted genetic material). Files, possibly computerised, are associated to this assembly of biological material, and are composed of the data which is essential for it to be exploited (origin of donors, genealogy, clinical and biological data). Samples may have been provided by healthy volunteers or the sick for clinical purposes, research projects, or judicial activities"[*]. To the above must now be added embryonic samples for the creation of stem cell banks.

The duties and rights of the banker, librarian, or curator; must be defined, since the choice of a designation must reflect the solutions brought to bear to solve the legal or ethical problems.

CCNE excludes from the scope of its proposals biolibraries constituted for judicial purposes and will restrict the present Opinion to the scientific and medical matters within its purview.

3. Goals pursued in the use of collections

The third reason for providing collections with a new status is to legitimise their use for medical or public health reasons, or for research, epidemiology and population genetics, whilst ensuring that this scientific finality is well defined, and that there is adequate separation between such activities and other types of uses, in particular those based on genetic information.
The latter do raise some ethical issues. Either they are rejected because of the risk of negative discrimination which they carry, and therefore are prohibited by law or subject to a moratorium as is the case for reference to genetic data for employment or insurance purposes. Or they are legitimised by law for police or judiciary uses, in which case their purpose is to identify individuals.

[*] S. de Montgolfier – See above

If the scientific autonomy of collections is guaranteed and there is no possibility of cross-matching the data for other purposes, it is more likely that they can be put to harmonious and beneficial use.

However, even in an environment which is authentically devoted to the health and life sciences, there are still some doubts about the organisation of this autonomy, and they must be dispelled.

III – Status of the conservator or curator.

As a start, some consideration could be given to defining a legal content and status for the function of conservator or curator of the large collections.

This function has already been analysed in the charters and contracts drafted by the early initiators, such as the Généthon company itself, or in the description of the task to be carried out by the Centres for Biological Resources, or in the recent Sixth Framework Programme of the European Union.

However, by giving a legal standing to this status, it becomes obvious to everyone that this is not an ordinary activity, that it is not governed by freedom of enterprise, and that it is regulated, as is the case for the whole sequence of operations leading to the collection or the use of elements of the human body. It is not to be seen as an acquisition or as an appropriation of the collected elements and the associated information data. A new service is being created ; its framework must be defined.

This is the case because faultless quality, security, and monitoring must be provided and are the foundation of a certification system. Responsibility for this kind of reliability is a serious undertaking. **Banks must therefore be registered, possibly subject to prior authorisation, and in any case, function under supervision.**

The curator will be at the centre of a network of tightly managed rights and obligations. Upstream, there are the rights of depositors, consent, archiving queries, ultimate fate of the collections, so as to avoid both unregulated exchanges and irreversible losses of property. Downstream, there are conditions of access by researchers or industrial users to the material stored, and protection against attempted abuse or prohibited access.

This function must include a mediation or conciliation procedure to cope with possible difficulties and to protect both individual interests and those of researchers. The function of the curator could be either personal or institutional. What is important is that the various events – collecting, processing, storage (safety, destruction) and use – are connected within one single sequence.

The reimbursement of expenditure must be organised. This is not a difficult matter if the bank is a public institution. However, if private operators, be they associations or other forms of organisation, are running them, or if they are set up as a consequence of industrial research activities, there has to be a decision as to when financing is necessary. In any event it must be regulated by specifications.

As such, and also in the name of intellectual or industrial property rights, the activity of the curator or of his function are part of the debate on the exploitation of activities whose starting

point is a conscious or presumed donation at the time elements of the human body are deposited. This activity does not make any fundamentally new contribution to the discussion, but its insertion in a succession of operations must not lead to eluding the debate. On the contrary, defining the status of a curator helps to make it clear how that service fits into the sequence and its role in the financial exchanges involved in exploitation.

The components of a new framework must be defined in such a way that they are understood and applied by all the actors of a complex procedure : the person who is at the source of the sample, possibly a group or a community who are concerned, the authorities as representatives of the concept of a shared heritage, the scientific community, the authorities again but this time in the guise of regulators of the system. Although the definition of a status for banks is the starting point for dispelling doubts, CCNE does not consider that this is the most difficult problem.

IV – Individual consent.

Several causes of tension due to the creation of these large banks affect the rights of individuals. They are related to the evolution of the notion of informed consent, its adaptation to cope with the durable nature of the banks and repeated use of their contents, possible contradiction between security and protective measures and abusive use of the items collected, and finally, the view that individuals may have of their rights over such items.

For optimal use, biological samples must be capable of association with medical data, and in some cases, partial or complete lineages concerning the donors and their families. The scientific and medical value of such collections, in association with medical and genetic data drawn from previous studies, must not be reason for forgetting the extreme sensitivity of such material as regards the ethical principles involved – individual rights of privacy, autonomy, and dignity. Information of a medical or genetic nature in association with samples of biological material are at the centre of an individual's intimate organic personality and concern family lineage, ascendants and descendants. Sometimes, there is at this stage a problem due to discrepancies between biological kinship and kinship in the eyes of the law. This is a further illustration of how essential it is to take every precaution to respect the privacy and wishes of individuals.

1. The traditional form of consent

The issue of information and consent may seem at first sight to be quite straightforward ; recognition of those rights is generally acceptable. This procedural guarantee is approved both by those who subscribe to the unavailability of the human body, and by those who would claim an individual's right of ownership over those elements. A considerable number of national or international instruments state this requirement. As early as 1991, CCNE stated : persons who are sampled for the purpose of genetic studies must have given free, informed and specific consent. But to have given consent is not by any means a guarantee of absolute ethical protection. Some studies may be ethically ambiguous (for instance, investigating the existence of a gene connected to sexual behaviour, etc.) In order to obtain consent, the instigators of a research project must provide at least the following essential information :

- a description of the object of the research, with background information on the state of scientific knowledge;
- a presentation of the framework in which such research is to take place : medical and non medical staff, possible participation of industrial personnel;

- a description of the possible consequences of the research project as regards diagnosis, prevention, therapy, with specific information as to possible consequences for those participating in the study;
- use to be made of data collected - publications, patents, possible research and development agreements;
- the fate of samples once the initiators of the programme cease their research efforts. If research with different aims is planned using the same elements, renewed consent must be obtained with the same limitations as for initial consent.

This is indeed very specific, and interestingly, this meticulous analysis of the points to be included, is included in the more recent international texts (cf Unesco, Council of Europe, report written in Israel). One point is blindingly obvious : since there is banking involved, this information must be provided not only at the time of launching the first research programme, but also when the collection is deposited. It must be specific about the fact that there will be storage, and where it will be stored, and identify the persons or the structures who will be responsible for keeping elements and information; information must also be given on the expected length of time of conservation.

2. A new controversy is emerging regarding anonymisation, consent, and the right of recovery

Rules governing the accumulation and use of such collections must respect two principles, which are sometimes contradictory. One is that they should be put to optimal use to serve the community, particularly for scientific, medical, and public health purposes; the other is that in so doing, such collections should not be simply treated as though they were public property that could be somehow incorporated into the social and public fabric, or on the contrary, treated like merchandise. In other words, donors must be informed in broad terms of the type of study which their donations will be used for, and of the framework in which these studies will be undertaken.

If an ethical endeavour were to be content with this formal obligation and pay no attention to its practical implementation, it would be very vulnerable. Donors of cells, organs, and samples cannot be in fact informed of the entire future of their donation because no one has that knowledge and because the collection itself is only meaningful if it is lasting. Furthermore, the time at which the research project will need to analyse genetic characteristics is not known in advance. At some unforeseen point, the project can have an impact on the interests of third parties, or of descendents, or of siblings, or of a group sharing the same common genetic trait.

Obviously, the fact that the collection may well be kept for some time means that asking for consent every time it is used is not a very realistic option. The accountability of the initial author of the project becomes diluted, and even if it were possible to discriminate usefully among the projects those which deal with single gene diseases and those which do not, it would sometimes be rather difficult to locate donors whose consent would need to be renewed or rejected.

It would therefore seem reasonable to simplify the consent procedure.

In the first instance, it must be fully implemented at the time when the sample and its associated information data are banked. That is the time when copious information should be provided on projected uses, foreseeable duration, possible outcomes, and other persons involved.

As a second step, provided the person concerned agreed, it would conceivably be acceptable that should personal data be scrupulously anonymised, it could be used for subsequent research without renewing consent procedures. The principle of solidarity would in this case be a justification for concessions regarding the rules observed to safeguard individuals, but it would be true solidarity dependent on voluntary decisions.

However, to prevent any abuse, **all banks would have to set up some kind of consultative body**, that persons directly concerned with the initial banking procedure could address enquiries to. These persons would have been duly advised of this possibility, so that they could enquire at any time about the purpose for which the collection and the related information data were to be used. Although the use of results drawn from a genetic study to develop a marketable product or technique does not present insurmountable ethical problems, this possibility if it existed would have to be made known to those concerned, and they would have to give consent.

Another more serious difficulty is due to the contradiction between the need to find the persons concerned so as to access useful clinical data, or to give them the benefit of research results, and the requirement to protect them. **Technical developments in fact reinforce very strongly the need for confidentiality**.

The difficulty is not so much in the letter of the law, because all that was necessary is included or inferred very directly out of the privileged information rule in the doctor-patient relationship which applies to any sampling activity, or in the rules in the law dated January 6, 1978 regarding sensitive computerised data. The problem does not reside in whether any discrimination based on genetic characteristics can be opposed, since that is what both national and international instruments - the most recent being the Charter on fundamental rights of the European Union - already do. The problem, which in this case is purely practical, is to be certain that such rules of protection are in fact enforced, and the dimensions of the problem are amplified because the banks are large.

The first requirement is technology, because there is a need to protect effectively the anonymity of the data, and therefore to implement encoding procedures, which are now well tested techniques, but which in practice demand investment and training. It is also a question of choice. The traditional system of anonymity is challenged in two ways : by researchers and bankers on the one hand, who wish to keep for themselves the possibility, should there be some advance in genetic research, of returning to the clinical data originally collected, and on the other by groups of donors or patients who would want to claim for themselves some of the benefits likely to be yielded by the research. Now there is a contradiction between such possibilities and data security. CCNE considers that satisfying the second objective, anonymity, is the *sine qua non* condition for the development of large collections; this leads to some degree of moderation regarding the possibility of using identifiable individual data.
All of the professions involved with the banks must be made aware of the importance of this concept in the course of their training. The human origin of the deposit gives them responsibilities in this respect and the practical implications must be spelled out in detail in the regulations applying to the day-to-day operations of banks; such rules must be made known at the outset to persons who have consented to research or a deposit. Information on what would never be done in any circumstance (policing, cloning, etc.) must be given.

3.- Consent in the case of nation-wide collections

A set of new problems arise out of the fact that collection or storage may be of concern to a group or to a community; measures applicable to individual cases must be adapted. There is a collective approach emerging on the rights of persons who are the subject of research, and researchers working on population genetics are very mindful of this. The theoretical risk that very large collections giving access to individual genetic material, possibly at the level of an entire nation, as is being envisaged in an increasing number of cases, in a situation of national or international crisis, could fall into the hands of persons wholly indifferent to any consideration of ethical issues, or possibly even pursuing designs incompatible with respect for the freedom, autonomy, and dignity of fellow citizens, cannot be completely ignored. However, it would be unfair and unethical to burden genetic studies with such a degree of constraints as to the conditions in which they could be carried out, that it would become difficult or even impossible to undertake them. Such an attitude would be detrimental to scientific progress and to the benefits to be derived from it as regards screening and improved treatment for many diseases. At an international conference organised in Montreal in 2002, a set of principles were proposed and submitted for discussion on the web regarding ethical conduct to be observed by the scientific community when researching human genetics concerning populations : prior consultation of those populations, explanations to be provided, recruitment organised in such a way as to evenly distribute risks and benefits, security and confidentiality of data, respect of existing legal and ethical standards, sharing of information, transparency, contribution to the well-being of the population concerned and to that of mankind. The community of researchers are increasingly aware of issues and are beginning to adapt their practices accordingly, and this should be consolidated.

4.- Situations in which consent cannot be obtained directly

A particularly difficult problem is always raised in the context of international studies and collecting activities. Present day developments increase the number of situations when consent to the donation of biological material cannot be directly requested from the person concerned. Such is the case when the person is a minor or incapable of consenting. Traditionally, some trustworthy person is consulted instead, either a relative or someone who has been designated, with full precautions taken to protect the interests of the subject, and it is difficult to imagine any other solution being applied in the case of biobanks. But can one ignore the fact that the action concerned is complex, because the interests to be protected are not easy to determine or forecast as would be the case for some simple medical procedure ? And can one ignore that a collection based on samples from children necessarily carries knowledge about a whole future lifetime ? The question of stem cell collections opens the way to very specific problems which will be the subject of a separate Opinion. Furthermore, present developments bestow scientific importance on old collections long since archived, and it is difficult to accept that they might be the subject of all sorts of research without anybody's consent being asked at all. In the study of cohorts over long periods or of groups, it is customary to seek agreement with spokespeople and rules for their designation are the subject of intense debate amongst those concerned. Things are made all the more difficult because this kind of specific situation often arises in cases where the population concerned is particularly vulnerable or ill-informed. The need to put rules for consent and for requesting opinions from those concerned under the jurisdiction of mediating bodies, who are independent of the promoters of research projects, then becomes apparent.

5.- Consent, personal rights, and common use

Personal rights consist in not being obliged to participate - by making available physical elements or information, particularly bearing on genetic characteristics - in a collection operation for research or conservation., A corollary of that right is the right of withdrawal as

long as the information is not anonymised. This right could be extended to patients, in particular in the case of single gene diseases with representation by appropriate organisations, to gain priority access to the beneficial scientific fallout for their particular case. However, CCNE does not consider that the newly recognised importance attached to these elements and data should lead to moving any further in the direction of personal autonomy and giving to individuals a form of ownership of the physical elements sampled from their bodies, to be disposed of at will with the related data, or of fallout of research based on those elements and data. On the contrary, as regards the issues referred to in this Opinion, there is reason to state once more that they do fall within the scope of the principle of the unavailability of the human body.

If it were not so the question of who has the right to dispose of those elements and data would inevitably arise, so that there would be a risk of their becoming part of a commercial circuit and of possible claims from people or groups for a share of the expected profits. These are the very convincing reasons which led France to reject the recognition of such rights over the physical elements of the human body, and hence to demand that such activities be part of an ethical framework.

It now seems that for the same reasons, the rules of unavailability and non-commercialisation should also apply to the information, which should be deemed inseparable from the physical elements stored in the banks. Such a system has consequences which may lead at some time in the future to awkward comparisons with the situation in other countries for instance. Individuals may not request studies or conservation to be undertaken for their private consumption, as a precaution to safeguard possible civil rights.
However, to CCNE's thinking, the time has not come to recommend a complete philosophical change, not until banks connected to research have been endowed with a status and have attained operational maturity.

V – Rights to collected elements and information which the national community could feel entitled to.

1. – Use for the common good

Rules for the setting out of the conditions in which genetic studies can be undertaken using collections of biological samples must take into account the rights and duties of the various parties concerned. Genetic data is only meaningful for research if it can be pooled.
This is a further reason for not being over hasty in defining new rights for the sake of individual autonomy. It is likely that we shall soon come to envisage the idea that the banking of such samples and data could focus on the common good.

The origins of such use are to be found in the spectacular initiatives taken by some States, Iceland being a prime example, to embark on a systematic nation-wide collection of medical, genealogical, and genetic data. There are already some examples such as Estonia, Tonga, and within a public health system which is closer to our own, the United Kingdom.

Contents, and in particular the type of element collected, vary. However, their common characteristic is their size and the fact that some undefined but highly beneficial future use is expected. For this reason, these national banks are overtly referred to as a "resource". There is ongoing and thorough discussion as regards the nature of consent. It would be explicit in Estonia, Tonga, and the United Kingdom. For Iceland, it would be explicit for sampling, but implicit for medical data, except that the person concerned could, for a very short time,

exercise a right of withdrawal. The procedure, which is cumbersome and costly, may involve negotiated cooperation with a private company, exclusive access for a company called Decode in Iceland, and Autogen in Tonga, and access is not exclusive in Estonia. The Biobank project in the United Kingdom involves the participation of public sector researchers with a possibility of access for private sector researchers. As a consequence, these projects are considering, more or less overtly, some kind of return of profits to the population.

At present, the scope of such initiatives cannot be evaluated, since none of these projects have become operational. To their credit, there is the notion that there is a need for large scale investment in order to reap the full benefit of the genetic revolution, and that the countries which have prepared themselves to do so, will be at an advantage. On the debit side, there is truly cause to be worried about the idea that some profit can be drawn from such resources and that the people concerned are seen as mere gene donors in cases where no specific project acts as justification for addressing them in the first place. Clearly, the accumulation of a mass of data for reasons unspecified in the service of more or less accountable research is a risk as regards the confidentiality and the proper use of these extremely sensitive elements.

However, CCNE does consider that genetic science and the powerful technologies now available have opened up a line of exploration which modern societies should avail themselves of. The rights of individual contributers must take into account the fact that their contribution is valuable because it is pooled with others. Simply because the possibilities opened up by the new scientific advances exist, there is a duty of solidarity between individuals and between successive generations. These advances also give substance to the notion of a common heritage owned by groups of population, if not by all humankind. Prospects are sufficiently encouraging to justify that such advances should be shared and widely available.

2.- Guarantees

CCNE considers that some preliminary thinking is called for and that several principles could apply, the first of which would be to only launch such operations if there was some justification and very serious evaluation of what to expect from them. A second principle would be to submit such a project to public consultation for very open and competently organised discussion, following the example of the Human Genetics Commission in the United Kingdom which carried out for the information of the British public a very thorough evaluation of the Icelandic project. A third principle would be, in the French context, to restrict operations to a public promoter, which could be specially created for the purpose if required, so as to avoid upsetting the balance which keeps the human body out of the commercial domain. It might well turn out that French society could then accept the idea that the contents of banks are a form of scientific heritage which has to be pooled if progress is to be made. Such a concept should make it possible to find appropriate solutions to some of the problems raised in this report.

3. – Rights of the community

It is in the general interest that the benefits expected from research should be made available as quickly as possible. Therefore, whilst fully respecting the rights of initial investigators and of individuals supplying samples, measures should be taken to optimise the use of collections of biological samples. The collective interest may sometimes enter into conflict with that of other partners, such as the right of donors to be informed, and to non nationalisation or economic privatisation of their biological samples, as mentioned above. But there is also the community's right to avoid very large nation-sized collections from being used exclusively to

respond to the commercial interests of an industrial partner to whom exclusive access rights have been conceded.

VI- Researchers' new attitudes in a new context

The investigators of collections, practitioners, and researchers, whose talents for invention are at the source of these new advances, have lost a great deal of their liberty in the wake of inexorable developments, and must be helped to adapt to a new situation.

They work in a well regulated environment, in which they are expected to implement rules for the protection of individuals, organise their relations with the curator and other users, with the curator's assistance.

Initial investigators are academics and frequently devote considerable effort to collecting biological material for genetic enquiries : preparing the project, establishing precise inclusion criteria, organisation, maintenance and keeping ready for use the samples in the collection… In the circumstances, the demands of investigators for a reasonable amount of time in which they can, with all the means available to them, benefit from the scientific fruit of their efforts, are acceptable. However, this legitimate right may contradict those of participants in the collection to optimise the research which is being conducted thanks to their joint generosity. A compromise between these two types of legitimate interests can be a designation of the lapse of time during which investigators have privileged access to the collection they put together, and the moment when the collection must be made accessible to other teams, possibly in a more favourable position to conduct the research as it was originally designed, or any other research of the same kind as the one which was originally acceptable to participants.
Such notions would seem equally valid in the case of collections assembled by a pharmaceutical company with the help of voluntary donors, as required by national legislation. Whether investigators are from academia or industry, economic benefits accruing from products or processes based on results of research are naturally possible, or even sought after. Such a possibility must be explicitly described to donors providing samples when their consent is requested.

1. – Rights of depositors

The necessary consequence of depositors' rights is that the first initiators of research involving the collection of physical elements and data, have an obligation to specify the use to which they intend to put them. As long as they are put to that same use, promoters have a responsibility which they may wish to organise in contractual terms by sharing tasks with the bank. They may wish to relinquish that responsibility, but they then have an obligation to see to the fate of a collection which has scientific value. These efforts cannot simply come to nothing or just be allowed to go to waste. There has to be some obligation to organise archiving for collections which are sufficiently exploitable.

Some queries need answering for the benefit of researchers :

How would the filing of a collection and an extension of possibilities of use affect their intellectual property or patent rights ?

How can a choice be made or some balance found between giving priority to the depositor and organising generous access to valuable scientific resources ?

2. – Organisation of access

The crucial issue concerning access to the banks has not been settled. Two schools of thought are opposed :

- Controlled access is in fact what researchers have adopted so far. One expression of this thesis is to be found in the Généthon charter.
  The depositor of a collection signs a contract as a contributor, with the aim of determining the exact contents of the deposit and specifying that the collection was put together with due regard for the rules of consent. He may file without any intention of immediate use or he could continue research. A number of clauses protect the rights of depositors in the form of priority of use for a given number of years. In parallel, conditions of access are organised for other researchers. Concerns are recognition of the rights of initial depositors, recognition of the services rendered by the bank, and reimbursement of costs expended by the bodies who ensured financing.

- The idea of free access to DNA banks is spreading, because regulating access and restricting it to certain users can be seen as a source of discrimination against certain potential users and a curtailment on scientific exchange of information. But should free access be understood as access for all, i.e. equalitarian or even mandatory access, which does not in any way signify that free access means free of charge ?

Several models have been offered. No discrimination should be made within a given category of users, which would need to be defined by certain objective criteria (research quality, participation in certain types of research programmes, etc.) A more radical approach favours broader opening to, for example, the whole community of researchers. CCNE had already referred to this point of view in 1991; the Committee feared that appropriating genetic data for the use of a chosen few would in fact be an appropriation of the means for acquiring knowledge. The Committee stated that all research projects in the field of the human genome should have access to data bases.

This debate does not settle the difficulties in connection with transfer to the initiators of banks of intellectual property rights. Article 1 of the Directive 96/9/CE dated March 11, 1996, as transposed into French law on July 1, 1998, as regards the legal protection given to data bases, defines the latter as “a collection of works, data”. Protection by authors’ copyright refers to article 3 al. 1 if the bank is classified as a “work”, and its protection may also be provided by a “sui generis” right provided in article 7 of the directive. The consequences of this protection are that a legal framework is provided to support the contract between the person in charge of the bank and the user : the basis of the solutions to be applied must be clearly defined. The donors of biological samples have without any doubt the right to be informed of the immediate and deferred objectives of the collection, and of the way the collection will be used. Donation being, by definition, a voluntary action, these persons have also and very naturally the right to refuse sampling, or even, in conditions to be specified, to withdraw from a study, at least in its identifying phase. Donation is often bound up with an active commitment in favour of some specific research which is of special concern, or simply to promote science in general. In the first case, donors eagerly await research which can increase their knowledge and open the way to therapy to give relief to members of their family. In the second case, donors are aware that they are making a voluntary contribution to

scientific progress. In both cases, the researchers and structures to whom donations were entrusted, and probably also the community as a whole, are duty bound to guarantee that the research in question will be carried out in such a way as not to betray this trust. Should a first set of scientists take the initiative of assembling a collection, but were then not able within a reasonable time frame to make use of it, it would be necessary to codify the conditions in which the collection could be opened up to other teams of researchers in order to increase the chances of fruitful research. The above considerations seem just as valid when the initial investigators are academics, as when they are employed by a private research laboratory, as long as the latter has based sampling on scientific or medical objectives.

VII – Financial arrangements as regards collections

1 – Public or private organisations

Such arrangements can only be elucidated once a question of principle has been openly discussed. Should the activities of biobanks be governed by a public or private sector system, or should both possibilities be left open ? In France, at this time, the system is virtually part of the public or non-profit sector. This is because the sources of most of the "premium collections" were in the public hospital system. However, associations have now gained significant ground in this respect. The question arises of exchanges of material and information with foreign operators whose mode of operation is commercial. In the same way, public institutions do not hesitate to claim intellectual property rights or to file for patents in connection with research based on these banks.

The question of whether a bank can be a private institution is solved in the affirmative in major countries where genetic research is very advanced. There is an international trend in that direction. In the last five or six years, the big pharmaceutical companies have been setting up DNA and data banks as part of their clinical research. Others have gone even further with the constitution of specific banks for research on therapeutic targets or to constitute cell lines of embryonic stem cells.

2 – Industrial research, cognitive research

There are two major reasons for the creation of such collections : one is pharmacogenetic and concerns the drug under trial and modulating its action under the influence of certain genes; the other aims at discovering new "therapeutic targets". The first aspect is not really very different from any other industrial activity. The second, however, raises many an issue. First of all, the expression "therapeutic target" is fuzzy. If the purpose is simply to find genes whose variability could contribute to knowledge of the disease under study, this is general cognitive research, which traditionally is part of academic activity in a context of shared scientific knowledge. The resources used by private genomic laboratories, including the creation and exploitation of banks, are not to be compared with those of public sector activity. As it happens, private laboratories tend to keep their biological resources and their data banks to themselves for their own purposes, so as to guide genetic studies in the direction of the more lucrative diseases. The powerful bio-computerised genomic analysis tools are mainly developed in the private sector (using for the most part, for that matter, data and algorithms produced by the public sector). Such a situation could lead to a form of capture of this research domain by the private sector, and, because public and private strategies differ, the risk of impoverishment of scientific or conceptual quality

3 – Some principles of organisation

If it is felt that the precious resource collected from human bodies on the basis of consent given by individuals, must be used to set up broad cognitive strategies, and if one wishes to preserve the principles of unavailability and non-commercialisation of elements of the human body, then the situation has to be elucidated and ordered.
Useful lessons can be learned from studies carried out abroad. Although the economic systems differ, there is clearly no support anywhere for the notion that such activities should not be regulated by the authorities for the common good. A study carried out in Israel shows that this leads to drafting some form of specifications, which vary according to whether they are for the public or the private sector. The public sector is given the mission of carrying out the more general research work, and there are rules which govern the distribution and use for the common good of financial benefit generated by possible patents. Regulation of the private sector is based on specific projects being filed according to the rules which include codes of good conduct, and which are just as strict as public sector rules. They seek to define the protection afforded to the necessarily human sources of the elements conserved, and should thus help to create the climate of solidarity which the value of such collections justifies.

To sum up, **the first step should be to define the common obligations governing the status of curator, which would be identical for public and private operators, and for partnerships.**

In any event, curators are the keepers of a collection which in France cannot have been legally bought ; it is governed from the outset by the rules of unavailability of the human body and is not marketable. CCNE suggests that this line of reasoning should be complemented by stating clearly that the collection contributes to the constitution of a collective asset, that this resource must be collectively managed in a spirit of solidarity. This certainly does not signify that the work done to maintain that resource should be unpaid, nor that if a work of invention is completed and leads to the creation of a test or of medicinal drugs, that the normal financial consequences of this activity should be denied because the material was banked.

However, the need to organise this sequence of connected events adds fuel to the notion that any bank must be part of an accredited system. Such a system, which requires in-depth legal analysis, must deal openly with the matter of remunerating the conservation activity, and of the financial consequences of later uses. These consequences do not rest on the principle that the collection may be sold ; the law must therefore intervene to lay down a compromise solution.

Furthermore, because opposing interests have to be reconciled, it is likely that private collectors would have to make some legal application to file their material, and that DNA collected for private purposes should be made available for cognitive research, and thus serve collective interests.

From this analysis, one can draw the conclusion that in the general context of the status to be provided for biobanks, financial aspects must be included ; using the traditional public service management formula could meet requirements without isolating France from the international scientific community.

VIII – A responsibility for the authorities

There is no doubt at all that something must be done in the field of biobanks to reorganise their legal status ; the present formula is no longer a working proposition.

The authorities must take on a **function of regulation,** and there is no dispute in France that this is both needed and justified. It might well be that such a function should be undertaken by an independent authority, on the same model as the CNIL *(Commission Nationale de l'Informatique et des Libertés* – National Information Technology and Civil Rights Commission) so that there could be simultaneously a supervision of the physical samples which are banked and of the data of sensitive information. Such an organisation should include, in a way which requires agreement between the various government departments concerned, the structures set up to coordinate the Biological Resources Centres.

It should then be possible to give such a body, not only the power to authorise and supervise banks, but also the mission of **developing the practical arrangements required to solve the operating problems experienced by banks**. This would include, inter alia, a description of the techniques required to ensure the security and anonymity of collections, in all the fine detail referred to above, developing consent form models on the basis of prior practical research, analysing the basis for an evaluation of services rendered with a view to remunerating the function of "banker", etc…

The advantage of giving an institution the task of defining a code of good practices is that the outlines which it would produce could serve as a basis for exchange contracts until such a time as an international legal framework is devised. French operators would be committed to using only that system in the meantime.

However, the same public authorities would have to undertake a task which is unprecedented in our country **: that of adequately consulting and educating the public** about the challenges represented by these collections. A debate could be organised about the value of opting for large scale collections of the type under consideration in the United Kingdom, and about the guarantees, conditions of management, and justification for this pooling of human biological resources. If such a debate is undertaken early enough, and in the absence of any favourable or unfavourable preconceived ideas, it could help to prepare us for an international environment where such data will be, and must be, exchanged.

March 20, 2003

Annex 1

The profusion of initiatives, and the pandemonium of studies and commentaries might lead one to think that some new activity is seeking a path on virgin territory. Nothing could be further from the truth. In the French legal system, one point is clear. We are in a domain which legislators are intent on regulating. Neither the collection of elements, tissues, cells, etc. of human origin, nor the study of the genetic characteristics of an individual, nor the establishment of computerised files, nor the processing of the resulting information, are unregulated activities. Nor are they subject to the laws of marketable goods and services. On the contrary, several systems co-exist so that the same problems are approached from different angles which ignore each other. As a consequence, the French legal system is not based on the principle of personal autonomy nor on individual property rights over these elements and information data. But in a world in which trans border exchanges are a daily occurrence, we cannot ignore the fact that the philosophy of other societies does not rest on the same foundations, nor fail to see that in the absence of legislation, claims might well be made that rules governing trade practices are appropriate.

The medley of legal approaches which could be applied to these collections in France, forms a miscellaneous assembly, containing references to various principles, and nevertheless leaving loopholes, the least of which is that the function of curator is not regulated.

In chronological sequence, a collection is made up by taking samples during clinical or biological acts connected to diagnosis, treatment, or a specific research programme. The normal rules of medical practice apply and entail as of necessity the cooperation of the patient undergoing this procedure. Payment for the first step in the constitution of the collection is part of the medical procedure and is financed by the community healthcare system. If a research project is grafted onto that action, it is financed through a research contract, or becomes subject to the Huriet Law and the supervision of the agencies for the Protection of Persons. This system is to be modified as a result of the implementation of a new European directive relating to clinical trials.

This first set of rules means that there is a person who is in charge of a research project which requires starting a collection and consent from the person concerned by the project. No one wishes to see today's technical developments threaten the present two-phase system – clinical, then research – in which collecting physical elements and data and genetic research are still included. It is true that the analysis of a person's characteristics is only possible in circumstances provided for by law; but the law has specifically stated that for medical diagnosis and therapy and for the purposes of resulting research, it is a legitimate activity.

At this point, it is already clear that the system has its limitations as soon as the relationship between patient and physician comes to an end, or a given research project is terminated. It is not constructed to ensure the durability of collections and data, nor for giving the initial promoter any long-lasting responsibility in this respect. It was not designed to last, nor to cope with future prospects of scientific progress.

Conserving samples and connected information data is protected by law, based on two legal systems, the first of which relates to physical elements sampled and preserved, and the second covers the constitution of the resulting information data files.

As regards the first subject, a distinction has to be made at present between the general situation for research involving the use of elements of the human body, and directions specific to genetic research.

A first set of protective measures for the human body applies : they are contained in articles 16-1 and the following articles of the *Code Civil*, in particular article 16-10, and have to be complemented by the directions contained in the *Code de Santé* about the conditions to be observed when sampling and collecting tissues, cells, and other products of the human body. These are articles L 1241-1 to L1245-2 and 3 of the *Code de la Santé Publique* regarding scientific uses of cells and tissues. They are based on the principle of the unavailability of the human body, which is not to be included in any commercial transaction. They refer to articles 1243-1 and the following, for the purpose of notification, and the agency responsible for health products has a role to play if the establishment is collecting for its own projects. Furthermore, authorisation is also required if actual transformation or concession are involved. Securing consent from the person concerned is demanded by both the *Code Civil* and the *Code de la Santé.*

Directions specific to genetic research are to be found in a special section of the *Code de la Santé Publique*, in article 1131-1, where it says that outside of a judicial framework, examination of genetic characteristics or identification by genetic prints, can only be undertaken for medical or research purposes, and after consent has been given by the person concerned. In the following articles, which originated in a law dated May 26, 1996, a system of notification is outlined for such collections. As a result, informed consent is required, which entails a description of the collection project with details regarding destination.

It is by no means easy to evaluate the practical outcome of such measures. The decrees for the implementation of the law were long delayed; a commission of the Ministry of Health, with the task of accrediting practitioners and authorising laboratories to test for genetic characteristics only became operational in 2000. There is also a Clinical Genetics Steering Committee for developments in research. A more orderly view of the matter is to be found in the bill for the revision of the bioethics laws which is pending parliamentary decision. The fact that an examination of genetic characteristics can only be undertaken for certain purposes, i.e. medical or scientific research, is re-stated with vigour, as is the requirement for consent, and also that violation of these rules is punishable by law. The legal system applied to collections will very fortunately be harmonised, since article 1131-4 mentions the transformation and conservation of elements and products of the human body, including the constitution and utilisation of collections of human samples for genetic research purposes. A system of authorisation is to be used to ensure respect of these obligations.

It therefore appears likely at this point that collections, insofar as they accumulate physical elements, must operate in conformity with the principles prevailing in France regarding the unavailability of the human body and the fact that it cannot be the subject of trade, and that this also applies when collections are to be used for genetic research.

In parallel, however, the Ministry for Research has launched a call for bids for the creation of a network of biological resources centres. These are collections of physical elements, some of which but obviously not all, are of human origin. This system is supervised by a commission which is drafting a guide, known as the deontological charter. Since existing banks would stand to gain by official recognition and some financial advantage, the administrative departments in charge of research could incite them to notify their existence. Because of the

participation of already functional organisations, there is an ongoing discussion in practical terms regarding consent models or access to data. A philosophy is beginning to emerge, but there is no incorporation of previous rules. The whole procedure however is characterised by the fact that it concerns biological resources in their entirety, with no limitation to resources or data of human origin. Experience acquired for flora and fauna, where the exploitation of biological resources is encouraged, does not rest on the same presumptions of unavailability and non marketability which are to be observed in the case of elements of the human body.

The other approach which must be kept in mind is connected not to the physical elements themselves, but to the information data which are intimately connected to them, in particular in the case of genetics. Banks will also work on filing and processing computerised data.

Banks fall within the scope of the law on information technology and civil rights, under the supervision of the CNIL *(Commission Nationale de l'Informatique et des Libertés*). As the data concerned was obtained in a medical context, they are considered to be sensitive and the problem has been considerably augmented by the emergence of genetics. The fact that some rules will apply because of CNIL case law, and be influenced by European law, will have to be taken into consideration. There is therefore reason to refer to the law dated July 1, 1994, on the subject of the processing of identifiable personal data for the purpose of health-related research, which modified the law dated January 6, 1978 on information technology, data banks, and civil rights, to a deliberation by CNIL dated February 4, 1997, and also to a European directive, dated October 24, 1995. The latter document is being transposed into French law by Parliament. An entire set of rules is emerging on confidentiality and safety of computerised processing, not under the control of the healthcare and research authorities, but under CNIL which is an independent body, Almost all genetic research projects will be supervised in this fashion.

In that complex construction, there will be controls at every step. The person or patient does not own the elements which are to be preserved. Research projects are to be notified or authorised. But the scope of the obligations on each participant in the phase of conservation of these elements and data – particularly if it is to be long lasting – is not clear from the kind of dialogue which should take place at the time of securing consent, so that some uncertainty remains. The foundations of the principles are subject to variation and interpretation. At the start, the traditional medical contract prevails. If research is to be viewed in the light of the physical elements, the principles of unavailability and non marketability of the human body apply. Securing consent is an indication that the element collected is a donation. Rules applicable to computerised files give the impression that researchers can do almost as they please as long as they ensure confidentiality and accept that the person concerned may wish to access the information which has been filed, or decide to withdraw from the research. These differences are accentuated when questions of intellectual or industrial property or remuneration of these diverse activities are raised. The rule of non payment prevails for the deposit of a physical element ; it ceases to be mentioned clearly when the subjects of processing the reference data or conceding the collections are raised.

Apart from the above ambiguities, it is clear that the framework proposed for the development of new technologies leaves a certain number of questions unanswered.

Annex 2

Biological samples and personal medical data as a national resource : some examples[*]

Gwen Terrenoire, CNRS
Assistante de recherche auprès du CCNE

Collections of human biological samples and medical data have existed for a long time in hospitals and research centres. Recently, however, with the help of their centralised healthcare systems, several States decided to organise the utilisation of such material on a population-wide scale ; if only because of their size, observers took an interest in these projects. The first cases to become known were those of Iceland, Esthonia, and the Kingdom of Tonga, whose populations are genetically homogeneous and are therefore preferential ground for research concerning certain diseases. The authorities in these countries asked commercial biotechnology companies to exploit these resources in exchange for various financial benefits. Other types of projects are in the process of elaboration, in particular in the United Kingdom, where public sector research is proposing two projects. One of them (BioBank UK) concerns about 500 000 people, and the other (NHS LifeHouse) bears on all those members of the population using the National Health Service, i.e. about 60 million individuals. For these projects, genetic diversity is at a premium.
A large number of more modest projects are following in the footsteps of these larger programmes. The population-wide approach is identical, and one feature is cooperation between public research and private biotechnology concerns, such as : UmanGenomics in Sweden, CARTaGENE in Quebec, Newfound Genomics in Newfoundland (Canada).
In this document we shall attempt to reconstitute the history of these major national projects and be making some comparisons or observations regarding the way in which they are likely to materialise when the time comes. The only project to be operational at this time is the Icelandic effort.

I. The Projects

Iceland

Iceland was the first country in the world whose Parliament decided to grant access to medical data concerning its population and exclusive rights to exploit them for financial profit, to a private biotechnology company called deCODE Genetics.

DeCODE Genetics was created in 1996 by an Icelandic physician and researcher who was working in the United States. His initial strategy was to come to an agreement with Icelandic practising physicians to arrive at a collection of DNA samples from patients suffering from certain diseases. Patients – about 20 000 individuals – gave explicit consent. These samples were combined with a genealogical data base containing files for 600 000 Icelandic nationals, dead or alive, and their family connections, so as to group patients into extended families. After encoding the data, genetic link analyses were performed.

The second strategy, which required parliamentary authorisation, was a project for the creation of a central bank of health data derived from the medical files of the population and transmitted in coded form by those practising physicians who were willing to participate. This project will be financed entirely by deCODE Genetics. The draft bill was submitted to Parliament in March 1998 without any prior communication to the public. It was modified by

[*] Report drafted early 2003

a second draft in June 1998, and finally a third version was adopted in December 1998 under the name of **Act on a Health Sector Database Act no. 139/1998**. Originally, it was intended that there should be "presumed" consent from the population for the use of personal data, with no possibility of refusal. This latter point was modified after strong protest from the medical professions and other groups, but the principle is still that consent is presumed, unless an intention to opt-out is expressly stated. There is no time limit to this right. However, the data pertaining to deceased persons who had not opted out when they were alive cannot be withdrawn. By December 2000, about 20 000 Icelanders had decided to avail themselves of opting-out rights. The law states that an exclusive license of exploitation will be granted to a single private company, and that access to data by researchers who are not employed by that company will be negotiated between parties concerned. In January 2000, the Ministry of Health announced that the license had been granted to deCODE, so that they will be able to link the data in the bank to the genealogical and genetic data they had already collected. DeCODE has announced several objectives : genetic link studies, development of diagnoses and drugs, improvement of Icelandic health management.

In 1998, deCODE signed a contract with the pharmaceutical company Hoffmann LaRoche for the development of medicinal drugs for about a dozen common diseases, on the basis of the Icelandic data.

The next phase consisted in collecting tissue, cell, and blood samples from the population. The **Act on Biobanks n° 110/2000,** which entered into force on January 1, 2001, bears on collection, use, and conservation of these samples in a biobank. The principle of presumed consent is applicable if the sample is collected in the context of a clinical test or treatment. However, if sampling takes place for research purposes, consent must be free and informed.

In 2002, deCODE signed another contract, with Merck this time, to work on the subject of obesity, again on the basis of Icelandic data.

Estonia

According to the Estonian researchers who are the promoters of the Estonian Genome Project, the objective is to gather together into banks the phenotypic and genotypic data regarding the Esthonian population so as to conduct research on common diseases and improve the management of patients. The State hopes to improve the economic competitiveness of the country by developing sectors for genomic research and high technology, and by creating new specialist employment opportunities as well as new products and services.

The **Human Gene Research Act, 2000,** is concerned with the collection and processing of data, and the protection of participants; it does not regulate research activities which are subject to other national and/or international legislation.

The central bank for genetic data will be established using blood samples from three quarters of the population. The whole operation is to be supervised by an ethics committee. The bank data is confidential, but the promoters consider that it is essential for the public to receive a maximum amount of information on the creation and organisation of the bank, and considerable efforts will be made to communicate with the public. Several opinion polls have demonstrated that the public is in favour of the project. Clinical files and genealogical information will be collected. The data and the samples, after anonymisation, will be the property of a foundation, called the Chief Processor, created by the Ministry of Health and a consortium of Esthonian researchers who are promoting the project. This body has the task of organising the sampling procedures, encoding, storing, destroying, and distributing genetic data, encouraging genetic research, collecting data on the health of the population, and using

the results of genetic research to improve public health. It can grant non-exclusive licenses to companies or researchers who wish to access the encoded data for research purposes. Estonian researchers will be granted access almost free of charge. The rights of donors are clearly described: confidentiality as to their identity; voluntary donation; the right to request data destruction; the right to access their own data stored in the bank; specific, informed, and voluntary consent. All samples must be stored in Estonia.

The project will be financed by a variety of sources, both public and private. The public share is to decrease gradually.

The law includes an article which prohibits any discrimination as regards employment and insurance.

Tonga

In November 2000, an Australian biotechnology company, Autogen, made an announcement on the Australian stock exchange regarding an agreement they had signed with the Ministry of Health of Tonga for the creation of a genetic data bank using samples harvested from the population, in order to identify genes involved in some common diseases. According to that agreement, the DNA samples remain the property of Tonga, but Autogen will have exclusive access to exploit them commercially. A year earlier, Autogen had signed a cooperation agreement with Merck Lipha, the pharmaceutical company, which produces drugs to treat diabetes.

To demonstrate the ethical nature of its project, Autogen published on its Web site a declaration of intention called *Ethics Policy for Genetics Research involving the use of biological materials collected from the people of Tonga*. This document includes several articles on the respect of subjects (prior information, voluntary participation, informed consent, respect for local customs, security of samples, confidentiality of information, anonymity of information), refers to principles of benevolence and equity (sharing profits). However, there is no provision for sanctioning any violation of these principles and some observers consider that the Declaration is worthless. Autogen has promised to finance the creation of a research laboratory and to contribute to the health department's budget.

The project attracted hostile reactions in 2001, in particular from movements defending human rights and democracy, and from the Pacific Council of Churches. The latter has published a declaration which has been widely circulated[1] in which the rights of the peoples of the Pacific to the moral ownership of their heritage are stated, and it defended the principle that consent must also be obtained from the family group and not just from the individual concerned. It wants the government to consult the population before taking decisions which could have an impact on their rights and that legislation should prohibit inter alia exploitation and bio-piracy for the sole benefit of commercial entities.

At the time this report was drafted, there was some uncertainty regarding the status of this agreement, since the Ministry denied signing it. Furthermore, it would seem that Autogen have given up their project in Tonga. Its declaration of ethics, which was displayed on the Autogen web site up to November 2001, has since been deleted. However, groups opposing the project have been unable to obtain precise information from Autogen.

The United Kingdom

BioBank UK (initially called **UK Biomedical Population Collection of 500 000)**

This is a research project proposed in 1999 by the Medical Research Council (MRC) and the Wellcome Trust (WT). The plan is to create a collection of biological samples from 500 000 volunteers aged between 45 and 69, who will be recruited by their attending

[1] *Bulletin of Medical Ethics*, March 2001.

physician if the latter is participating in the project, and to combine these with personal health data contained in medical files (which have existed ever since the creation of the National Health Service), so as to study the separate and combined effects of genetic and environmental risk factors (including life style, physiological and environmental exposures) of common multifactorial diseases affecting adults. Unlike the Icelandic, Esthonian, and Tongan projects, genetic diversity is a requisite. Data on life styles of subjects would continue to be collected for several years. There are also plans to possibly exploit the collection through an epidemiological study of the immune response to infectious diseases. Several centres will be collecting the samples, and researchers would have access only to data and not to samples. Access by private corporations would be possible on a non exclusive basis.

The document "*Draft Protocol for BioBank UK, a Study of Genes, Environment and Health" (February 2002)* describes the project in detail. Because of its scope and duration, it should make a contribution to future international research. The protocol calls for a financing submission for the first five years, but initial follow-up has already been programmed for ten years. Cooperation with industry is referred to in the context of translating scientific results into products and innovations of potential benefit to the population. One section deals with the ethical aspects which include prior information about the nature of the project, expected constraints, informed consent, confidentiality, and a risk/benefit analysis.

Before launching the project, the promoters have commissioned two studies, the first of which bears on the Icelandic project[2], the other being a series of enquiries to ask a group of doctors and several groups in the public about which conditions they think should be satisfied for this project to be acceptable to the public[3]. The conclusions regarding the study of the Icelandic project were negative, and there was emphasis on the fact that the public had been denied any information before Parliament voted.

The Human Genetic Commission contributed to public awareness by asking for opinions regarding the use of personal genetic data. The results of that enquiry were published in a report, *Inside Information, Balancing Interests in the Use of Personal Genetic Data* (May, 2002).

NHS LifeHouse Project

This initiative is part of a larger project aiming to modernise the National Health Service's system for keeping medical files. It was proposed by the House of Lords Select Committee on Science and Technology in its *Report on Human Genetic Databases* (March, 2001). This report recommends a population oriented approach for the collection of health data. The project itself would consist in creating a computerised database containing the health data for the entire population (60 million) in the National Health Service since it was created. Several objectives were declared : improve healthcare, supply a research resource, improve the management of the healthcare system. The text does not mention the issue of explicit consent from the population and does not seem to have had the benefit of public debate before the House of Lords formulated their report. It recommends presumed consent from individuals, approval for secondary research being the purview of a Data Panel. Genetic research is not a significant component of the project.

Public discussion is ongoing : a report on the protection of patients' personal data was made public in January 2002[4]. This latter document sums up the ethical and legal issues to be resolved. It opts in favour of a prior public consultation, in conformity with the Data Protection Act (1998) which states the requirement for reinforcing constraints on informed consent.

---

[2] **H. Rose**, The Commodification of Bioinformation : The Icelandic Health Sector Dababase, 2001.
[3] **People Science & Policy Ltd**., BioBank UK : A Question of Trust, 2002.
[4] **NHS LifeHouse**, Protecting named and anonymised patient data – consultation on an approach, 2002.

Québec

The **CARTaGENE** project was initiated at the end of the 90s by a group of researchers who were members of the Network of Applied Genetic Medicine of Quebec (www.rmga.qc.ca), in cooperation with the universities of the Province. These researchers wished to benefit from the genetic context which is particular to Quebec, since there is homogeneity in the region, and heterogeneity in Montreal, and explore the links between genetic heritage, environment, and health, in particular as regards cardiovascular diseases, mental health, and cancer. They expect participation from a representative sample population of 50 000 adults aged 25 to 75. Participants would be recruited on the basis of a list supplied by the Quebec sickness insurance system subject to authorisation being given by the provincial commission for access to information. Each participant would be asked for free and written consent before providing information to a professional health carer regarding medical history, life style, and habits. A blood sample would be taken for the purpose of DNA and serum extraction. All data would be anonymised.

In June 2001, the organisers of the project convened a semi-public workshop to examine scientific, legal, ethical, and social aspects. Their plans include initiatives to ensure that the public, the media, and all groups concerned get full prior transparent information, which would become accessible once the project is funded (public consultations, permanent jury of citizens).

In April 2002, in spite of support from Genome Quebec, CARTaGENE was not accepted by Genome Canada, which is the federal body in charge of financing genomic research in the Provinces. It would seem that this decision has interrupted (or possibly stopped completely) the implementation of this project.

However, even if this project gets no further, the international community will have gained because of the launch, on the occasion of a conference on the subject of population genetics (in Montreal, September 2002), of a presentation by RMGA of a Statement of Principles on the Ethical Conduct of Human Research Involving Populations (cf. site www.rmga.qc.ca *).*

II. Comments

1. A perusal of these projects shows that there is **no single model**. Everyone has their own configuration (promoter, objectives, proportion of private interests, funding, population concerned, rules of access, nature of consent, property of data, role of parliament, possibility of profit sharing…). The only common ground seems to be the existence of a national health system covering the entire population.

2. All the projects have encountered **difficulties** initially. There are several kinds of difficulties : in Iceland, despite the law being voted in 1998, it was only by the end of 2001 that doctors, government, and deCODE agreed on twelve years of cooperation. In Tonga, it would seem that Autogen have withdrawn following protest by influential groups in the population. In Esthonia and the United Kingdom, funding difficulties are slowing down the launch of the projects. Financial survival is even more of a problem for "small" projects, e.g. the interruption of the Quebec project.

3. Social acceptability

The Icelandic project has been the most controversial in this respect because the public was not associated with the initial phases of submission to Parliament. It nevertheless was able to retard the adoption of the law and obtain a modification in the final version. In spite of guarantees provided by law, many observers believe that it will be impossible to protect the privacy of citizens in a small country where everyone is related to everyone else. Groups

opposing the project in Tonga also seem to have discouraged Autogen, but they are convinced that other private companies will try to exploit their biological resources at some future time.

The BioBank UK project drew lessons from the debate in Iceland, and launched several public consultations on the social acceptability of its own project. They also financed a critical analysis of the Icelandic experience which should help them to avoid some of the pitfalls. However, the British have several institutional consultative layers, in particular the Human Genetics Commission, which includes representatives from civil society. This does not seem to be the case in other countries.

Those in charge of CARTaGENE are planning to include measures for prior information about the project for the public and the media, and to give supervisory access to the public as the project progresses.

4. Resources, exploitation, benefits

Promoters and observers of the national projects describe them as **"a resource for research".** A resource is something which is exploited, which raises the question of who by, and for whom ? The Icelandic resource will be constructed and exploited exclusively by a private company, and benefits in favour of the population are expressed in extremely general terms. The resource in Tonga, will be set up by Autogen and exploited exclusively by that private company. Its ethical charter, however, commits it to return 1 to 3% of the profits generated by research to the Tonga population. The British resource (BioBank UK) and the Esthonian one are public projects which will be exploited by academic researchers and by private commercial firms although the details of cooperation contracts between the public and private sectors are not yet known.

5. The idea of a **genetic heritage**, as a kind of property belonging to the population was promoted by the Pacific Council of Churches which opposed the Tonga project. In the case of Iceland, the data was sold to a private company. In Estonia, the data – once it is anonymised - becomes the property of a publicly controlled entity. This latter is responsible for collecting and processing the data, although it is free to delegate certain procedures to other processors at a lower level.

6. The resource is often presented as a **key to power in the hands of the country concerned** in its dealings with other countries. This notion is very clearly expressed in the presentation of the Estonian project : "Estonia wishes to be an actor in the competitive race for genes market, in its own original manner". The project is to improve the competitiveness of the Estonian economy (through the development of research technologies and infrastructures, investment in high technology, creation of jobs and products and services of high intellectual value ; the development of biology, bio information technology, and biomedicine, linked to social sciences). It should also improve the management of the healthcare system; increase the self-understanding of Esthonians regarding their own health…" The same rationale is to be found in the protocol of BioBank UK.

7. The issue of consent

Iceland : presumed for medical data, with a possibility of withdrawal, (except for those who have died before expressing refusal).

Estonia and Quebec : informed consent after prior information.

Tonga : prior information before securing consent. Observing cultural specificities. Participants may decide whether the use their data will be put to is acceptable.

BioBank UK : explicit consent to participate in the project and authorise the use of data already existing in medical files. Application to join will be formulated by attending physician

participating in the project. Full information will be provided several weeks before securing consent.
NHS LifeHouse (United Kingdom) : consent presumed.

8. Limitations on data exploitation :
Estonia : The data must not be used for discriminatory purposes.
Tonga : Protection against any form of wrong is a priority (psychological, sentimental, anxiety, worry, and economic and social discrimination) but the declaration of ethics gives no indication of how this is to be achieved.

9. Bank supervision
Iceland : Data Protection Commission, National Bioethics Committee. The controversy on the lack of consent led to setting up a complicated supervision system involving five separate bodies which guarantee that the managers of raw data, the date encoders, the regulating agencies, and the license holder are quite separate. This development has improved public confidence in the project.
Estonia : an ad hoc Ethics Committee.
Tonga : an Ethics Committee is planned. The project will also need to be approved by the International Diabetes Institute Human Ethics Committee.
BioBank UK : the project will be evaluated by the UK Multi-Centre Research Ethics Committee. Exploitation possibilities by private companies will be evaluated by the Scientific Management Committee in charge of the project.
NHS LifeHouse : Multi-Centre Research Ethics Committee ; Medical Data Panel.
Quebec : the directives drafted by RMGA supply the general outline. As for any research involving human beings, the project will need to be approved by an Ethics Research Committee.

Annex 3

Collections of human biological samples : some figures

Gwen Terrenoire, CNRS
Assistante de recherche auprès du CCNE

There are several kinds of human biological samples appropriate for biomedical research : DNA, blood, tissues, cells, cell lines, or serum/plasma. The following data is to illustrate the numbers involved in established or projected collections.

Existing collections

United States of America : By end 1998, it was estimated that the total number of biological samples was 282 000 000, with an addition of twenty million new samples per year.

- 96 000 000 samples are stored in two large collections, the *National Pathology Repository* and the *DNA Specimen Repository for Remains Identification*

(Source : National Bioethics Advisory Commission, 1999)

- **France**[*]
- Généthon : 46 000 ;
- Centre d'étude du polymorphisme humain : 15 000 in 2002 ;
- Institut biologique de Lille : 15 000 in 2000 ;

Iceland : 20 000 samples stored by *deCODE Genetics* in 2002.
United Kingdom: 350 000 samples in the *Police National DNA Database* at end 1998.
Sweden : 3 000 000 samples stored by *Eurona Medical/Gemini Genomics* ; 100 000 in *Umea Medical Biobank/UmanGenomics*.

Collections projected for 2002

The figures given below represent the target number of participants.
Estonia: 2/3 of the population, i.e. 1 000 000 persons for the *Esthonian Genome Project ;*
Iceland: the whole population, i.e. about 280 000 persons for the *deCODE Genetics project ;*
Latvia : 60 000 persons for the *Latvian Genome Database ;*
Norway: 200 000 persons for the *Conor* project and 270 000 for the *Moba* project, which are the central components of the *Biohealth-Norway* project *;*
Quebec: 50 000 persons for the *CartàGène* project *;*
United Kingdom: 500 000 persons for the *BioBank UK* project *;*
Tonga : the whole population, i.e. approximately 108 000 persons for the *Autogen* project;
Europe : 400 000 persons for the *European Prospective Investigation into Cancer and Nutrition (EPIC)*

[*] Source : Thèse Montgolfier, 2002.

Comité Consultatif National d'Ethique pour
les Sciences de la Vie et de la Santé

Nationaler Ethikrat

Ethical issues raised by collections of biological material and associated information data : "biobanks", "biolibraries"

Joint document

1 – Introduction

This document reports on a series of joint discussions, in 2002 and 2003, between the German National Ethics Council (Nationaler Ethikrat or NER) and the French National Consultative Ethics Committee for Health and Life Sciences (CCNE) on the theme of biobanks. The two exchanges and debates on this important theme showed that both Ethics Committees were concerned with similar issues as regards the collection, processing, storage, and use of samples of human origin and the associated information data. Both considered that clarification by legislative authorities was needed. Despite the fact that legislation diverged to some extent in the two countries, efforts to elaborate satisfactory responses and propose solutions can be anchored to standards which both countries recognise as fundamental.

As a consequence, it seemed appropriate to append a jointly written supplement to the Opinions drafted respectively by the two Committees.

The object of this supplement is to outline a joint conception of the problems raised by biobanks. The differences or variations which may appear in the recommendations formulated for the attention of legislators in each of the two Opinions, or the possible disparity in emphasis for some of the aspects of questions under discussion, are due to national contexts prevailing in the two countries.

Biobanks or biolibraries are private or public institutions which are designed for the long term storage of samples from the human body and of the personal information data associated to these samples. By human samples, are meant cells, tissues, blood, and DNA as a medium for genetic information. The data and information cover both the genetic characteristics of the persons concerned and information regarding their state of health or their life styles. The specificity of biobanks, which are the subject of these Opinions, resides precisely in this dual nature : the collections, that is either the biological material or the resulting information data, must be treated as one whole; and since any collection can at some point serve for genetic research, the system governing biobanks includes directions concerning genetic research. Another fundamental aspect is the computerised processing of this data and information, as well as the electronic communication which can establish connections between them and transmit them in a much more rapid and effective manner than used to be case, so that there is a radical transformation in the scale of useful capacity.

The Opinions drafted by the two Committees do converge on the same issue : the biobanks which are created for medical research, and for medical research only. The word biobank is taken as meaning entities managed by the public or the private sector, for the purpose of long term storage of samples taken from the human body, and the storage of data relating to the persons concerned, in other words information regarding the donors of the collected samples.

2 – The need for an Opinion

The sampling, conservation, processing and use of the biological material collected in biobanks, as well as the concurrently collected information concerning persons, are long established practices. However, a technical revolution is upon us. Collection and comparison on a massive scale of these elements and information data permit associations which in the long term lead to the acquisition of valuable diagnostic and therapeutic learning, and gives these elements and information data a hitherto unsuspected worth. The formation of large biobanks will represent a considerable asset for the development of life sciences, medicine, medical research, public health, and demographic information or population genetics.

However, this highly promising progress is viewed with some apprehension and mistrust by the public. Such reactions are due to the fear that data and biological material could be used for other purposes than those the donor expected. Understandably, donors of biological elements and information collected for a medical research project could be upset if they were later made available to police or justice departments, or an employer, or an insurance company. Nor must research projects themselves use elements and data for purposes which donors could not possibly anticipate when they gave consent, and which they might legitimately object to.

Clearly, the creation of biobanks leads very naturally to the transmission of elements or information to third parties. Furthermore, more often than not, information regarding donors is not only relevant to their own body samples ; it may have a bearing on those of their relatives, or of even larger population groups, or of the entire population of a country.

The French and German national ethics committees agree on the fact that the ethical and legal challenges connected to biobanks are legion and demand the creation of a framework whereby new and coherent regulations, on a national or international scale, can be implemented. Persons who contribute to such progress by donating elements from their own bodies must be

protected by clear rules against abuse of data which is of direct concern to them personally. However, there is also a need to refrain from hampering technical development with excessive regulation. The framework still to be defined must reconcile those two considerations.

3) Taking into account a sequence of responsibilities

The expression « biobanks » covers complex activities, integrating four domains which have already been detailed above, i.e. collection, conservation, processing, and the use of biological material and data. All of this must be regulated in a comprehensive framework which is designated by the name of biobank. Nevertheless, it is worth noting that these different activities each raise specific problems which require appropriate solutions. At each point in the sequence, the actors may be different people. There are those who collect tissues, data, and information, and others manipulate the body substances which are collected, label them, encode them, anonymise them, or re-identify them. All of these activities must however be regulated coherently, with due regard for technical advances. It is for this reason that the « sequence of responsibilities » must be defined, without any gaps or interruptions, and why an entity responsible for the regulation of the whole process must be appointed. The model appropriate for this role is an administrator (or curator) whose characteristics, functions, and obligations, remain to be defined.

4 – Free and informed consent

The issue of consent is at the core of the discussion on the ethical and legal regulation of biobanks. The principle is so fundamental that it must structure all of the activities of biobanks previously mentioned (collection, conservation, processing, utilisation). The two Committees found, during their joint discussions, that efforts to define the exact scope of free and informed consent raise a great many issues.

The problem that arises at this point is to discover what were the research objectives that the donor of bodily substances gave consent to. Were they exclusively diagnosis and therapy, in other words the primary objectives which led to collection in the first place, or also all the other possible scientific goals, which were not predictable earlier because they emerged from the cognitive dynamics of the research process ? Should donors trust the integrity of the research process and consent from the outset to elements of their bodies and connected information being used for any or all research objectives that a scientific investigation can generate and which are not predictable ? Should consent be a « blank cheque » ? And for what degree of data identification would that be valid ? Should donors be given a range of options to choose from as regards consent ? Are there limitations to the amount of information which can be given to them and can they consent to accepting a form of information which by nature is imprecise ?

The two Ethics Committees are in any case aware of the difficulties arising out of two necessarily antagonistic viewpoints as regard free and informed consent : on the one hand, the best interest of patients and the protection of their personal data, in the name of which one might be tempted to erase as quickly as possible the link between biological material, corresponding information, and an identified individual ; on the other hand there is scientific interest which justifies the possibility of being able to locate the person concerned so as to correlate his/her particular circumstances to new results. The person concerned may also wish to access these new results. In view of this complex situation, the ethics committees feel

that for biobanks the conditions of free and informed consent should be more clearly delineated.

Undoubtedly, the information to be provided, when deposits are made into the bank, and before any research projects are launched, must be particularly precise and elaborate, and must take into account that a full sequence of follow-on events may occur. As a result, it is quite impossible to prepare a single abstract template for the consent form, but there is a need to consider and harmonise a range of possible procedures, and to have them drafted and evaluated by an entity specifically tasked to do so.

Both CCNE and NER insist on the need to organise a documented debate in their respective countries.

5 – Functions of an administrator

Because the organisation of biobanks is such a complex matter, it is important to provide for an administrator (or « curator »), whose functions would coordinate the various phases of the bank's activities and who would be accountable for the respect of certain instructions.

CCNE and NER agree that the administrator's task is not limited to the mere management of the physical elements and information data accumulated by biobanks. He must be the central point of exchange at the hub of the system.

Nor is the function limited to making sure that in each of the four domains, ethical principles and legal provisions for implementing them are respected ; there is also a need to verify that sampling procedures and the utilisation later on of the physical elements and the personal data comply with the form of consent which the donor chose to adopt. The administrator must also control access to biobanks and ensure that elements and data are only made available for the purpose of scientific research and in a manner which complies with conditions stipulated by the donor's consent.

Furthermore, the administrator's duties include supervision to ensure the hygiene, safety, and more generally, the reliability of the collection. Finally, he must ensure that there is no possibility of abuse, in particular if the biobank's existence is ended. For the accomplishment of some of these tasks, it may be advisable to provide for the creation of an independent ethics entity.

6 - New outlook on solidarity

Biological material and resulting information can be extremely valuable for biomedical research when they are collected and preserved in large quantities. Modern means of data processing on a substantial scale have opened up new possibilities. So far, France and Germany have not formulated any plans for the creation of a national biobank, as has been the case in Iceland, and has already begun with the help of sizeable resources in Esthonia and Great Britain. Nevertheless, these possibilities deserve to be discussed very openly. At a time when vast quantities of data are collected for the purpose of biomedical research, a whole new field of problems appears regarding solidarity, altruism, and justice.

The principle whereby the human body cannot be marketed, which is in force in many countries and which is recognised by both France and Germany, for reasons which go way

beyond the issue of biobanks, prohibits making available any elements of one's body to a third party for remuneration. However, the two committees broached a subject which sometimes arises on the international forum, i.e. the sharing out of benefits – or even of profits as is sometimes said – which proceed from collection and conservation activities. Both committees consider that if there were recognition, for persons who contributed, of a personal entitlement and a right to financial return out of these results, there would be a risk of undermining the principle whereby, since the human body does not fall within the scope of commercial transaction, there is reason to consider that elements and data can only be collected by the bank as a result of a donation in favour of research. However, there could be a discussion as to whether certain very specific categories of patients should be allowed to claim some form of priority access to particular therapies discovered because of the biobank's existence, or else that some of the results of these activities could contribute to collective health or welfare schemes. These subjects deserve to be discussed in more depth and matured, but the effort made to constitute large collections using elements of the human body, with the consent of those concerned, should lead to some pooling of the means to collective progress.

7 – Conclusions

This analysis shows that, despite some differences, there is a need in both France and Germany, to elaborate a new regulatory framework covering collection, conservation, processing, and utilisation of the elements and data assembled in biobanks, and the development of research including protection of individuals. Since these activities are by no means restricted to national boundaries, efforts to achieve these ends must also be international.