

OPINION N°83**Generalised prenatal screening for cystic fibrosis****Membership of the Working Group**

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On December 19th, 2002, Professor KITZIS from the Poitiers CHU (university teaching hospital) referred to CCNE on the subject of screening mothers at the beginning of the 2nd trimester of pregnancy for the F508del mutation in the CFTR gene. The aim of the screening programme is to offer prenatal diagnosis in order to identify at-risk couples. The object of the intended pilot study is to assess if it is possible and acceptable to use such a test before perhaps making it available to all pregnant women. The F508del mutation, when homozygous or in combination with other mutations of the CFTR gene, is the most frequent cause of cystic fibrosis. The condition is, more often than not, very serious and invalidating. At this time, no decisive treatment is available, and when a foetal diagnosis is made, the mother is authorised to request termination.

International debate regarding prenatal screening for cystic fibrosis remains open and there is no definitive conclusion (see in annex an analysis on this subject by G. Terrenoire).

- I – The context of the referral.

A serious genetic disorder. In France, cystic fibrosis is one of the most frequent of the severe hereditary diseases (almost 200 births a year); it is a multi-systemic ailment caused by mutation in the *cystic fibrosis transmembrane conductance regulator* (CFTR) gene that leads to an anomaly in the movement of chloride across cellular membranes. As a result, among other effects, there is an accumulation of mucus in the lungs and the pancreas provoking severe respiratory and digestive problems.

Prevalence in France is about 1/5,000 births, with considerable regional variation. In Brittany, prevalence is 1/2,000, whereas in the Paris area and the south of France, it is about 1/10,000. It is estimated that, at this time in France, almost 2,000,000 people are heterozygous carriers of a mutation in the CFTR gene, and 5,000 suffer from the disease.

Transmission is autosomal recessive. Producing a child with cystic fibrosis is therefore a **1/4 risk** for two heterozygous parents carrying a mutation in the CFTR gene.

The F508del mutation is the most frequent of the mutations causing cystic fibrosis. In France, it represents 70% of them. Almost 1,200 different mutations in the CFTR gene have been identified since it was discovered in 1989. The available genotype detection kits cover about 30 mutations. There is not always any close correlation between the genotype (combination of mutations) and the phenotypes (clinical manifestation of the disease). The homozygous state for the F508del mutation is generally associated with a severe early onset form of the condition, but other mutations may be associated with moderate or late onset forms.

The natural history of the disease varies considerably. Two thirds of patients are diagnosed before one year of age, sometimes at the neo-natal stage on the occasion of the appearance of meconium ileus, but this is increasingly rare now that ultrasound screening is performed during pregnancy. Using molecular diagnosis an increasing number of rare forms characterised by moderate symptoms (sinusitis, bronchitis) have been identified. Sometimes, they are only diagnosed when the patient is adult, following pulmonary or digestive problems, or male primary infertility, or more recently female reproductive problems. Early therapy and improved care have progressively increased life expectancy of patients from 15-20 years to 30-35 years on average.

Social representation and experience of the condition have now increased to some extent through television broadcasts with a large audience (Telethon). However, the underlying genetic data does not seem to be accessible to such large audiences at the present time.

The special characteristics and severity of cystic fibrosis are such that this genetic disease is greatly feared. There is no known cure as yet, and all that can be done is to **prevent** infections. Some organ grafting (mainly lungs) is sometimes possible. The relative rarity of the disease and the increase of life expectancy should not be a reason to forget the distress of affected children, adolescents, and young adults, and also of their families, nor that therapeutic progress is still modest. At present, it is estimated that at the age of 20, patients will have spent on average 2 years of their lives seeing physiotherapists, and almost 3 hours of every day in therapy. This is a considerable strain on families and it is very difficult for sufferers to comply with the constraints of school and the workplace.

Screening takes place in varied circumstances:

- Systematic *neonatal* screening has been performed in France since 2002, although this is not the case in many other countries. This has been a factor in organising early management starting from birth with the aim of improving life expectancy and quality of life. The first stage of screening is a biochemical test (assay of a pancreatic enzyme, immunoreactive trypsin) performed on a blood sample taken at birth. If an abnormal trypsin level is detected, molecular diagnosis based on the detection of mutated alleles is performed (the kit includes 20 mutations at present and is to be replaced shortly with a 30-mutation unit). Children for whom a CFTR gene mutation is evidenced will then be given a sweat test in the month following their birth, the results of which in some cases are not easy to interpret¹. Understandably, this rapid succession of urgent testing, biochemical to begin with and then genetic if there is the slightest doubt, and then again biochemical, with parents being asked to report back at short notice with the child, leads to a considerable amount of anguish. It should be underlined that more than 90% of children undergoing these test procedures turn out to be healthy... An ongoing evaluation of psychological tolerance for this systematic neonatal screening process should help to gain a more precise appreciation of how cautious implementation should be.

It is worth noting that neonatal screening makes it possible to detect indirectly two heterozygous parents before a new pregnancy and possibly to supply genetic information to the family as a whole who would then be able to benefit from genetic screening testing.

Consent to neonatal screening and the way it is done do raise some new issues. It is only for molecular screening that there must be prior written consent. As it happens, consent is sought in a **climate of foreboding** because it occurs very soon after biochemical screening for which the amount of information supplied is limited. The genetic information provided after testing is of a complex nature and sometimes parents find it difficult to understand. This may lead in particular to a feeling of stigmatisation because of a heterozygous status, which has just been revealed and may sometimes cause a modification of the parent-child relationship, although this may fade away later on.

Planning for the possibility of prenatal screening does involve being aware of all the ramifications.

¹ Sweat is collected after placing an electrode stimulating perspiration on the forearm. This painless test takes 5 minutes. The amount of sodium in the sweat is measured and it should normally be less than 40 mmol/l. The level is higher in the event of cystic fibrosis.

- *prenatal diagnosis* is presently offered to at-risk families when a child has cystic fibrosis or when one of the parents is aware of being heterozygous. The screening, which is part of the process of dissemination of genetic information starting with the sick person (see CCNE's Opinion n°76²), can lead, after testing the father, to performing trophoblastic biopsy and possibly to termination of the pregnancy.
- discovery of maternal or paternal CFTR gene mutation may lead to considering a *pre-implantation diagnostic* procedure before transferring into the uterus embryos obtained through in vitro fertilisation. But the fact is that this is a taxing, and sometimes very taxing procedure for the mother, and that 3 in 4 of the embryos are unaffected.

This means that these screening procedures, which may be viewed as a “personal” or a “family” matter, if they are “extended” to a given population, or “generalised”, become so many adaptations to specific situations.

The proposal to extend prenatal screening to a sample of a random population, which is the subject of this referral, raises the major issue of generalisation to a given population, or even in time, to the population as a whole. Such screening would have the following consequences:

- to enable diagnosis before the neonatal stage of a serious condition that can no longer be prevented;
- to giving informed parents the possibility of making an enlightened choice regarding recourse to prenatal diagnosis that could be followed by information about the possibility of terminating pregnancy.

As proposed, the protocol would consist in screening for mutation F508del in the mother during the 2nd trimester of pregnancy. If the F508del mutation is not found, the probability of the unborn child being affected is extremely low. If the mutation is present, the father is then tested for the presence of mutation F508del and for other mutations over the whole of the CFTR gene by scanning. If that test is negative, the risk of an affected child is 1 in 3,300 because of the possibility of other non-tested or unknown genotypes. If the test is positive, the risk becomes 1 in 4.

What can therefore be considered as “effective” prevention does raise some ethical issues that CCNE has identified. Some of them refer to the protocol as such, but most have more general implications that will also be examined.

- II – Analysis of the proposed protocol

I – Technical aspects

Reliability. Testing of maternal and then paternal blood samples is a completely innocuous procedure. Identification of the F508del mutation is technically reliable. However, a large number of other rarer mutations (30% of known mutations) could be involved. So despite the reliability of the test, it does not totally cover the risk and will not eliminate the need for neonatal screening, because the presence of mutations, which are not accessible to the test, and of a child born with cystic fibrosis cannot be altogether excluded. If one accepts that mutation F508del represents only **70%** of the number of mutations affecting gene CFTR,

² Opinion N°76. Regarding the obligation to disclose genetic information of concern to the family in the event of medical necessity.

seeking out that single mutation in both parents would mean evidencing only 50% of the at-risk situations ($0.7 \times 0.7 = 0.49$). For that reason, the male partner of a woman diagnosed as positive would undergo a more exhaustive testing procedure for mutations in the CFTR gene; however, this would still only permit a maximum detection of 80% of at-risk couples.

Predictive characteristics. **The molecular test cannot predict with certainty the severity of the disease.**

Accessibility, cost. The test's supporters commend its accessibility. An assessment of the global cost of extending the test in the prenatal phase, and of its possible economic "profitability" as compared to the particularly heavy expenditure required for looking after cystic fibrosis patients throughout their lives, is a matter for conjecture.

Population for analysis, delimitation, extension.

The protocol covers a non-targeted population as is appropriate to mass screening purposes. However, the following comments would apply:

- Populations are very heterogeneous. That being so, it is permitted to wonder whether there is a threshold risk figure, which justifies mass screening. Would that figure be 1/2000, 1/5000 or 1/10000?
- The protocol suggests combining prenatal screening for cystic fibrosis and trisomy 21. However, the way in which the public perceives trisomy 21 and genetic diseases differs radically. As a consequence, associating several screening procedures with such diverse connotations simultaneously during pregnancy (or at different times as could be provided for in a modified version of the protocol) could lead to serious confusion. The risk of amalgamating screening for cystic fibrosis which is a monogenic recessive genetic condition, with trisomy 21 which is a disability resulting from a chromosomal anomaly, must be emphasised.

Epidemiological outlook

As regards the recently introduced practice of generalised neonatal screening, epidemiological knowledge about cystic fibrosis would be enhanced by prenatal screening insofar as healthy heterozygous carriers would be systematically tested, women in particular. This actually raises the question of choosing the gender, women rather than men. A negative test for the father would suffice to exclude any risk for 1 in 4 of children. But it is easier to test mothers because they are the ones who seek prenatal healthcare.

Even if prenatal screening opens up the possibility of reducing prevalence of the disease, the results to be expected are bound to be limited by the existence of a small, but irreducible, proportion of mutations that remain undetected by molecular tests and by the impossibility of predicting with any certainty the status of the unborn child on the basis of its genotype. **The very concept of "eradication" of the disease is thereby void of any meaning.**

Implementation of the study.

A fairly considerable workload will be generated by the management, as is proposed in the protocol, of a group of 3,000 women (30 women a week for 100 weeks), and then of their partners, to arrive at an annual discovery rate of about 3 couples with a 1 in 4 risk of having a child with cystic fibrosis.

2 – Legal considerations

French law regarding genetic testing. Rules for genetic testing are stated in decree 2000-570 dated June 23, 2000 which sets the conditions for prescribing and performing an examination of a person's genetic characteristics:

- Information to be provided prior to free and informed consent;
- Requirement to secure the consent of a child's parents or guardian before studying a child's DNA;
- Requirement for authorised institutions and practitioners;
- Communication of results by the prescribing physician in a clear and appropriate form on the occasion of a personal medical appointment;
- The right not to be informed of the results;
- The results to be kept for thirty years.

Such conditions would seem to be achievable in the event of a protocol for genetic testing of the mother and then the father, but they have not all been explicitly provided for in the protocol now under examination.

Possible request for termination of pregnancy: the verified risk of cystic fibrosis, "a disease of particular severity and incurable at the present time", is generally recognised as giving access to this possibility in conformity with French law.

Is this the beginning of a eugenics policy, which is contrary to French law? Clearly, screening aimed at **systematically** eliminating the birth of a child suffering from any particular disease would be of that nature. However, the plan here is to give women all the available information so as to avoid the possibility of their giving birth to a severely stricken incurable child without having been warned of that eventuality. It is essential above all to ensure that couples do have freedom of choice in a specific context. This is in fact the general purpose of reproductive medicine, be it based on biological and/or ultrasonic data. The pertinent issue is rather the extension of screening to other diseases for which the frequency of heterozygous carrying is fairly close to that of cystic fibrosis. It is possible that in the future, identical questions are asked for 2 or 3 other genetic diseases on the occasion of wider-reaching screening efforts. That is why this question is important.

3 – Psycho-relational consequences of uncertainty

Information to parents: the successive phases from the offer of screening to announcing the results.

The entire process and its different phases are as many events in the relationship between the investigating physicians offering the procedure and the women and men concerned. In other words, the information given at the outset and during the follow-up of the women in the study cannot be "neutral". The information will be provided and received in a particular context, specific to their plans for parenting, and therefore on very sensitive ground. In particular, the following moments are critical:

- the initial offer is to be made at a fairly advanced phase in pregnancy (14 to 17 weeks of amenorrhea, week n)³, which is really very late for any exploratory procedure on either foetus or mother;

³ An amendment proposed by the authors of the protocol would no longer link the two screening processes – trisomy and cystic fibrosis – so that a blood sample could presumably be taken less tardily.

- the announcement (in week n+1) of the result to pregnant women, which in the event that it is positive, leads to seeing both parents, with a genetic test offered to the father (n+2);
- the announcement (in week n+3 or 4) of the results of the father's test and of possible risk to the foetus;
- trophoblastic puncture which also represents a risk and cannot be a peaceful episode;
- so that it is only at 18-21 weeks of gestation, after a lengthy period of uncertainty and anxiety, that a woman who has been informed will be able to ask for termination of pregnancy for medical reasons, if she so decides.

This is far from being a dispassionate and easy progression, and is in fact a stressful and disquieting time in the life of the family concerned. It requires meaningful and specific medical attention. But in fact the proposed protocol is extremely, or even totally lacking in this respect.

The protocol's information form does not describe the disease, does not specify the time lapse between medical appointments, mentions only very sketchily termination of pregnancy, does not reveal the objective of the pilot test, does not mention the circular which governs the performance of a genetic test procedure, does not consider the possibility of the test being refused.

Finally, one might well have doubts regarding the possibility of an erroneous perception of absolute reliability of the test on the part of those being tested. As has been mentioned above, if the father is not a carrier of the most frequent mutations, he may carry rarer mutations so that the child turns out to have cystic fibrosis, and complaints of medical negligence or incompetence will ensue. In the same way, a pregnant woman screened as negative, the father of whose child is an unknown carrier of the F508del mutation, may herself be a carrier of a rare mutation. The child will be born with cystic fibrosis which may lead to similar complaints. In other words, screening may be either reassuring or worrying, but cannot provide certainty, either positive or negative. The difficulty of putting that message across is probably not negligible.

Clearly, turning this kind of screening process into a routine and systematic procedure will not be compatible with the complexities of comprehension, the lateness of decisions to be taken, the excessive apprehension caused by the simple fact that one is a carrier of a mutation, all of which can certainly be explained to one person. **However, if screening is generalised, it is much more likely to be a source of confusion than to facilitate understanding.** This has already been noticed at the neonatal stage.

4 – The social perception of the choice between termination of pregnancy and the birth of sick children

Image, stigmatisation. The French population does not have a clear picture of cystic fibrosis. The condition has been the subject of prime time television broadcasts, so that there has been every opportunity for vast audiences to grasp the facts as presented by moving reports of personal experience. However, there has been no spontaneous demand for screening.

Women who have undergone screening procedures in the circumstances described above, and who have turned out to be heterozygous carriers, are satisfied with being given this information and of the possibility of a prenatal diagnostic procedure in order to avoid the birth of an afflicted child. However, only rare studies have been made of the anxiety experienced by these women while they await the results of screening.

Two complementary observations on this subject were made:

- certain countries, where medical tradition is particularly focused on genetic issues, have in the last few years been practising this type of prenatal screening followed by the offer of termination of pregnancy for medical reasons; the approach has been cautious, but evaluation shows that there is increasing acceptance; the families consulted have chosen what they see as the safer option;
- on the whole, one could fear that in future, if people were born with that condition which would mean that their parents either eluded systematic screening or refused it, they would be the object of increased social stigmatisation. It is also quite possible that children with cystic fibrosis might see as extremely offensive that their very birth is now viewed as being inappropriate...

- III – Ethical issues arising out of the protocol

A certain number of ethical issues become visible following the analysis above.

Although the matter under consideration here has some specific characteristics, the general recommendations made by CCNE in its Opinion n° 46 dated October 30th 1995 on the subject of genetic screening, have some bearing. They made the six followings points which could serve as a reference:

1. Requirement that the person tested have “as complete an understanding as possible of the consequences of his decision to accept the test or not”;
2. Medical confidentiality must be observed as regards third parties, including other members of the family;
3. Information on personal identifiable data and computer storage must comply with legal rules and CCNE recommendations;
4. Agreement with persons concerned regarding the use made of results;
5. Approval procedures for the reagents used in tests;
6. “Basic” medical genetics training to be given to health care providers with the object of ensuring the quality of medical information provided to those concerned.

As regards the proposed protocol, CCNE has given particular attention to the following difficulties, which are less concerned with scientific or legal considerations than with medical ethics, particularly as regards the relationship between investigators and their subjects of observation.

Consent: this is more complex than is generally realised. It is sought at various times and on several occasions: when pregnant women are asked for samples, then when fathers are approached, and then again for the possibility of a foetal test. These contacts, which may be followed by consideration of whether a termination for medical reasons is to be decided, certainly justify the need for genetic counselling. However, it will probably be difficult to make it perfectly clear to all mothers and fathers the exact significance of a heterozygous status, and all the more so because as the prenatal diagnosis comes very late in the day, it may well be a major cause for anxiety. For that matter, hoping to get that message across to the general public so that it is completely understood and common knowledge is probably wishful thinking. Similarly, it will probably always be fairly difficult to explain how a risk of 1 in 3,300 if the mother alone is a heterozygous carrier, becomes a risk of 1 in 4 if both parents are

heterozygous. In the circumstances, one may wonder whether consent will ever be sufficiently informed to be of real value. Taking a blood sample at 14 to 17 weeks of amenorrhea, i.e. late in pregnancy, would be reason enough to provide specific information. In fact, the *information sheet* proposed by the protocol has many gaps, as has been noted above. Finally, the most enlightening information must be supplied to the mother for her consent to termination to be as free as possible.

Screening the father is more complex than would seem. If, as proposed, the procedure is sequential, i.e. performed after the discovery of F508del heterozygous status in the mother, awaiting the father's results can be particularly nerve-racking whereas the probability of discovering the mutation in the father is close to 1 in 30.

Other strategies could be proposed with the object of detecting at-risk pregnancies for prenatal diagnosis. The blood sample could be taken at the same time for both partners. The test would be done for the mother. If it is positive, the test can then be done for the father. However results would be given to the couple, and not to the individual, so as to avoid anxiety while awaiting the result. Or else, tests could be performed simultaneously, instead of sequentially, for both partners without waiting for the mother's test results. The cost of screening would simply be doubled. However, it must be noted that protocols based on the couple are contrary to French law which requires individual genetic testing.

If both parents are found to be heterozygous carriers for a mutation of the CFTR gene, prenatal diagnosis is proposed. In 1% of cases, trophoblastic sampling damages the foetus so that pregnancy is terminated. The risk linked to the intervention therefore leads to a termination of pregnancy of healthy children, as is also the case in screening for trisomy 21. In fact, because mutations in gene CFTR are recessive, 3 in 4 of future births will be healthy individuals although both parents are heterozygous for the disease. There is a risk that discovery of heterozygous status could lead to an inflation in the number of requests for further examination from individuals who are worried by the possibility that their partners might be carriers of an unknown or rare mutation.

The prospects of a medical and anthropological objective extended to a whole population.

What are the expected advantages and justification of a pilot test involving 3,000 women? In view of the epidemiological data that the extension of the neonatal test has already provided, the major advantage lies elsewhere. It could be, however, the possibility of evaluating difficulties connected to performing the test and its acceptance by patients, how much time has to be spent by healthcares on supplying genetic information and matters relating to psychological tolerance for such testing, in comparison with studies carried out in other areas or abroad. It should therefore focus much more on these matters rather than on the collection of scientific data for which it will not contribute any new information. It would, for instance, be very useful to test the way in which information is understood as transmitted by various actors, and the psychological tolerance thereof.

Another interest served by this kind of pilot test would be to compare the effects of non-targeted as opposed to targeted transmission of information. Extension of screening to a general population raises the issue of the possible discovery by chance of mutations in the CFTR gene in families where the risk had remained totally unknown. This could then be the cause of irrational anxiety and incomprehension about a pathology that is of course serious, but arises with a frequency of about 1 in 2,000 to 1 in 10,000. It would be significant to be able to compare the reactions to such discovery in uninformed populations with those of populations already aware of the relatively high risk of onset of the disease.

It should be noted that there is an **almost total absence of French studies concerning the psychological aspects** (acceptance by individuals, psychological tolerance, comparison between targeted and non-targeted information) of genetic screening tests. Such studies have been undertaken in other countries and they are our only source of information. However, the results of these other studies need not necessarily coincide with the French situation, since the social and cultural context, the relationship to disease and to medicine are always specific for a given country. It would therefore be very useful to encourage French studies of this description.

Economic and financial aspects. Generalising prenatal diagnosis would be quite a costly undertaking (about 100 million Euros). The cost of existing neonatal screening is approximately 7 million Euros. It is true that the cost of care for a child with cystic fibrosis is considerable (evaluated at about 23,000 Euros per annum), but thinking along purely financial criteria in itself raises difficult ethical issues⁴. Although it is clear that prenatal, or even pre-conceptional screening should be encouraged in families who already have had a child suffering from cystic fibrosis, it is no less clear that generalised screening in present circumstances would appear to be an extremely costly exercise, for a truly uncertain benefit and in ignorance of the effects of such a scheme.

Conclusions regarding the protocol

CCNE has already remarked that the protocol is lacking on various essential points. These gaps constitute a major ethical objection to any implementation in that form.

The protocol's worth would **rather be in the direction of anthropological and psychological objectives than epidemiological or cognitive research**. It only becomes significant in generalisation, so that our thinking was based on that viewpoint which is justification for the reservations expressed above.

- IV – General points raised by the proposal.

Examination of this protocol has led CCNE into considering the whole issue of an extension of prenatal screening, and remarking that there are several degrees in that process:

- for a given disease, there is a choice to be made between either a relatively exposed population, which can therefore be targeted, or the population as whole.
- generally, the question arises of what diseases would call for an extension and according to what criteria.

This raises a certain number of further questions:

1 – Would this be participation in a eugenics policy?

If one sets out to prevent any unforeseen birth of children suffering from cystic fibrosis, and therefore to embark on mass screening, then the issue of whether it is possible to provide information on an entirely risk-free basis must be addressed. Today's society considers that progress in molecular biology is such that the birth of a child afflicted by any kind of severe pathology, of which the parents could have been forewarned, is ever less acceptable. As a result, we are confronted with a contradiction between a perfectly legitimate fear of allowing a new form of eugenics to emerge, and the no less legitimate temptation to

⁴ CCNE will be considering these issues in the near future in an Opinion on the subject of taking economic criteria into consideration when making medical decisions.

take advantage of progress in molecular biology to avoid the grief of giving birth to a severely handicapped child.

2 – Are we opening the floodgates of unlimited routine screening for all genetic diseases?

The limits of screening are not just quantitative; they are also qualitative. Mass screening for certain genetic diseases in the neonatal phase is of great value for the effective prevention of the consequences of those diseases; this is for instance the case for hypothyroidism or phenylketonuria. For what reasons should generalised screening for another genetic disorder be prohibited or authorised? This question, which arises in connection with screening for cystic fibrosis, could be extended to other pathologies.

3 – If a technique is available, should its **use be generalised to the population as a whole?**

This raises an ethical principle. Certain countries have launched exhaustive controlled screening programmes justified by the very pronounced prevalence of a given disorder in the population to be screened, for example thalassemia in Cyprus or Tay Sachs disease in Israel, as a result of some kind of social pressure by the group. Generalising such activities for low or moderately prevalent diseases is hardly conceivable and it is therefore necessary to be extremely vigilant on the issue of whether the side effects of screening do not turn out to be more of a disturbance than they are worth.

4 – Is this a **real priority as regards public health and is the cost-benefit ratio acceptable?**

In this regard, the notion of priorities needs to be addressed. In order to tackle a public health problem, a prerequisite is to have available a simple and unambiguous solution and to provide easily understandable information, leading to clear, non-stressful and effective courses of action. It is obvious for example that systematic neonatal screening for hypothyroidism, phenylketonuria, and congenital adrenal hyperplasia serve to take highly effective preventive action. In the case of cystic fibrosis, the predictive character of prenatal testing and the difficult task of communicating complex genetic information to parents, are substantial obstacles. Furthermore, care must be taken to remember the discrepancy between the sometimes dramatic severity of this disorder and its actual prevalence. A fundamental question, as always in matters of public health, is to be clear about whether we are dealing with collective or individual prevention; it is essential to compare the investment required for creating a generalised prenatal screening system and the investment required for organising increasingly effective management of patients. It is to be noted that systematic registration at national level of children born with cystic fibrosis is well on the way to completion thanks to the coordinated networking organised by the Cystic Fibrosis Resource and Competence Centres (*Centres de Ressources et Compétences de la Mucoviscidose/CRCM*).

Generalised prenatal screening could not obviously do away with the need for neonatal screening because of unknown mutations. The situation would therefore be prenatal screening combined with neonatal screening.

5 – Is it possible to supply parents with comprehensible information in a generalised setting? Who are the people who could provide it, and how would they be trained?

Parents must be able to fully exercise their freedom of decision. The tenor of information and the quality of the process of imparting it to those concerned are of paramount importance. In the present state of medical practice, it is unlikely that anyone could guarantee that this quality would always be optimal. Furthermore, the side effects of screening are probably extremely heterogeneous which is good reason to carry out structured studies, better suited to persons being tested than to purely scientific considerations.

Conclusion and recommendations

Prenatal screening for mutations in the CFTR gene is entirely justifiable in cases where there is a family history of cystic fibrosis or if one of the members of the couple is known to be heterozygous. It should be encouraged before union or conception for at-risk families, and it may be defensible in areas where the mutated gene has high prevalence. However, generalisation to the population as a whole raises problems which are not only ethical, but also scientific, legal, and economic.

Such screening would involve a large number of uncertainties.

- **Uncertainty** as regards the possibility that the child's mother or father are heterozygous carriers of an undetected mutation.
- **Uncertainty** about the severity of the disorder, even with homozygous F508del mutation or trans heterozygous situations with other mutations.
- **Uncertainty** on the risk of foetal death of a "normal" child, brought about by trophoblastic sampling.
- **Uncertainty** in neonatal screening about the final and absolute interpretation of sweat tests which may remain doubtful.

It may seem logical and rational to use scientific knowledge and technological progress to full advantage to prevent a serious disease from appearing, but the risk of excessive and futile screening must be kept in mind.

Generalised prenatal screening cannot therefore be attempted before a solution has been found to the problem of communicating high quality information about the disease and its detection, as present deficiencies on this score in neonatal screening have demonstrated. This would require **considerable investment in genetic counselling** which is not the case at present. Supposing this were done, there is still the problem of inducing unjustified anxiety at a really late stage in pregnancy, and therefore the possibility that the parent to child relationship may suffer disturbances out of proportion with the real risk of cystic fibrosis appearing in the future child. The timing of screening remains a fundamental issue. Should one wait for pregnancy before taking any action? Would it not be preferable to act before union or before conception? If this is a desirable objective, it is unrealistic to suppose that screening could be generalised, and all the more so because of a rather odd fact, which is that, some women conceal their heterozygous status when they are not pregnant, which reveals an instinctive self-censoring attitude regarding this information. This latter point means that generalisation would be a fallacy.

CCNE considers that implementing a generalised prenatal screening system for cystic fibrosis raises the issue of its possible eugenic connotation. Although such screening is not a true public health issue in the present state of epidemiological knowledge, it does provoke thoughts about the secondary consequences of apparently innocuous actions. The major problem is that efforts deployed on screening could be to **the detriment of the sick** whose need for solidarity from the community has increased because their lives are now prolonged. Patients are crying out for **active research** on how to deal with their condition. Generalised screening could absorb resources to the detriment of this research. **Progress in this respect is possible** and does not entirely consist in gene therapy.

Finally, the recurrence of these debates on screening compels us to raise the substantive issue which arises out of the knowledge that it is always difficult to reverse the situation once

screening is initiated. Therefore, preliminary reflection must be very soundly argued before moving from targeted screening to generalised screening.

CCNE believes that a circumscribed study, with specific objectives, based on a limited population sample, taking into account social, psychological and economic risks, could be considered. However, it does not believe that as matters now stand, generalised prenatal screening for cystic fibrosis should be encouraged at the present time in France.

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ANNEX

Generalised prenatal screening for cystic fibrosis: the international debate

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As soon as it was announced in 1989 that the gene for cystic fibrosis (the most frequent of the genetic diseases) had been cloned, the question of how this new knowledge could be used to prevent the disease was addressed. Several approaches have been implemented in countries where prevalence is high: population, prenatal, or neonatal prevention. The first of these consists in circulating information about the condition, for instance in schools (Mitchell, 1993) or by the offer to screen healthy adult carriers in areas or countries with higher prevalence (Brock, 1995). With neonatal prevention, it is possible to identify at birth children who will at some later date manifest symptoms of the disease. In 2003, four European countries, France included, added this strategy to their neonatal test procedures (Inserm, 2003). The National Institutes of Health in the U.S., however, are not in favour of doing so (NIH, 1997). Finally, prenatal prevention can be achieved by diagnosing all foetuses or only those belonging to couples that have already had a child with that condition. This latter approach, justified by a consensus of professionals, is very widespread.

There is no consensus for the other approaches. Some of the American States have invested in systematic neonatal diagnosis programmes despite reservations formulated by the NIH (Wagener, 2003) whereas elsewhere, there is still debate over the value of prevention in the population or as a preconceptional approach (Mitchell, 1993; Poppelaars 2003; Henneman 2002).

Systematic prenatal screening of healthy carriers in couples with **no** family history of the disease combines population prevention with prenatal prevention. This has been a subject of ongoing discussion since the 90s, but is still not resolved. Some countries (Denmark, United States) have decided to offer the possibility systematically to couples as part of the routine pregnancy management procedures, and the United Kingdom is thinking along those same lines. Experts in other countries, in France in particular, are more reticent. Recent American recommendations evidence a significant change in the thinking of specialists (paediatricians, geneticians, obstetricians...) in a country where there is already a certain amount of experience in screening healthy carriers of other recessive disorders (sickle-cell anaemia, Tay-Sachs disease) in groups particularly prone to these diseases. In the following, we present this evolution on the basis of an analysis of many publications on this theme in the last fifteen years⁹.

Initial positions

In the early 90s, the NIHs did not recommend the launch of systematic prenatal screening until pilot testing had been done to obtain information on public interest and the clinical and psychosocial impact of such a programme (Statement ..., 1990). The American College of Medical Genetics and the American College of Obstetricians and Gynaecologists shared that reservation. (ASHG, 1992 ; ACOG, 1991). In Denmark, where the prevalence of a single mutation, F508del, is very high, the Danish Council of Ethics, 1993, requested that

⁹ Our bibliographic research has shown that the contribution of French speaking authors has been close to nil.

evaluation of the trials include ethical considerations as well scientific ones. They listed the information to be provided to those enrolled in trials and a further list of information to be collected at the end of the trial. Family associations, and Danish society which was in the majority in favour of elective termination of pregnancy if the antenatal diagnosis was unfavourable, supported the project. In Germany, however, the association of families concerned and professionals were very hostile. During that same period, other countries chose different prevention approaches. For instance, in France a neonatal screening programme was organised in Brittany, where cystic fibrosis prevalence is higher than in other parts of the country (Scotet, 2000).

Pilot tests

As a result of official encouragement for pilot testing in the United States and in Denmark, several projects were organised. Unsurprisingly, conclusions were in favour of a generalisation of antenatal screening. Reports displayed admirable unanimity in favour of prenatal screening. The following are some of the results supporting this position:

- couples with a child on the way were distinctly interested by the procedure when it was offered as part of ordinary prenatal management procedures;
- more than 90% of carrier couples accepted antenatal screening and the same proportion of parents of an affected foetus chose to terminate pregnancy. Couples opposed to abortion as a matter of principle did not accept screening. For example, the number of refusals was frequently high in the United States and always very low in Denmark;
- it was possible to provide adequate information to those who had been offered screening with the help of pamphlets, videos..., followed-up by contacts with para-medical personnel. At this point, it was not necessary to call on specialists to provide genetic counselling;
- psychological reactions in the event of a positive or negative result are limited and can be controlled.

However, there are also other observations that suggest a more complex state of affairs and could justify a more cautious attitude. Most of these are concerned with conditions allowing for autonomous and enlightened consent.

- prior information. Those in favour of screening suggest that this could be undertaken by para-medical personnel, whereas genetic counselling specialists are of the opinion that counsellors specialising in cystic fibrosis should be brought in, because of the complexity of the disorder;
- time required to communicate the information. Opinions differ: the range is a few minutes to an hour;
- content of the information. The use of pamphlets or videos as a first approach is generally recommended. There are differences of opinion as to whether there should be a systematic offer for an interview with a doctor, or whether it should be only by request. The problem of providing information about the condition that is both exact and balanced is raised in two studies (Loeben, Dierickx) based on an analysis of the information pamphlets;
- quality of the information process and retention by patients. Certain pilot tests show clearly that a percentage of up to as many as 50% of carriers do not remember the result of their screening;
- freedom of decision of the couples to whom screening is offered. The rate of acceptance depends on the manner, oral or written, in which the screening is

presented. It is much higher when consent is secured a short time before the screening procedure. It is significantly less when patients are allowed time, at home for example, to think matters over before giving consent. In certain reports, it was found that some women said they had found it difficult to refuse the offer;

- financial burden of screening. This is the other factor influencing the acceptance of couples. American HMOs (supplying health insurance to all the workers in a company) were pleased to report almost 100% participation; the same can be observed in countries where there is universal coverage for healthcare, Germany¹⁰, and Denmark for instance.

Finally, it has been noted that those in charge of screening programmes are more interested in the rate of acceptance than in the process for securing informed consent.

Evolution of official positions

United States

Following the publication of its reports, the NIHs modified their position during a consensus conference in 1997 (see National Institutes of Health, 1999). They recommended, *inter alia*, that antenatal screening be **proposed** to adults with a family history of cystic fibrosis, to spouses of patients, and to couples considering pregnancy. They also wanted screening to be **provided** to other people if they requested it. Taking note of gaps and uncertainties pointed out by those in charge of the pilot tests, the NIHs requested that screening be introduced gradually to ensure that participants could benefit from adequate information and appropriate genetic counselling. The points to be included in initial information were listed. Finally, it was considered essential to be able to guarantee to participants that their independence and privacy would be respected, and that there would not be any risk of discrimination or stigmatisation. The NIHs consider that the following points should be improved: quality of information (developing a model would be advisable); training physicians in genetics since they would be answering their patients' queries; new legislation to protect participants from social discrimination.

There were few immediate reactions to these recommendations. Only one author (Schmidkte, 1998) openly criticised them for the following reasons: there was still no explanation of why the rate of participation was sometimes very high; psychological and social risks were not considered; adequate structures for the information and counselling of persons concerned were not available. This author concluded that the recommendations were "at best, premature". Later, other observers noted (Farrell, Fost, 2002) that, even though the NIH report had not been of much interest to the medical and scientific community at the time, there would probably be more attention after the publication in 2001 of the directives by two initially reticent professional organisations (the American College of Medical Genetics and the American College of Obstetricians and Gynaecologists), for practical implementation of the NIH recommendations. These directives (American College ... 2001) have been very widely circulated to professionals.

The text of the directives list the criteria to be satisfied in putting together the instruments required for screening: good practice guidance for clinicians, pedagogical material for physicians and for patients, model forms to obtain informed consent, and standards for the laboratories analysing participants' DNA..

¹⁰ A single pilot test was reported for Germany (Jung, 1994) which was in opposition to the general hostility mentioned above.

A more restrictive distinction is made than in the NIH documents regarding those to whom screening should be **offered** (in bold in the document), and those to whom it might be simply provided (underlined in the text). The first category includes at higher risk couples (people of “Caucasian” origin, and Ashkenazi Jews. The second category includes couples of other racial and ethnic lower risk backgrounds. As regards the first of these categories, it is recommended that screening be offered when preconceptional counsel is given in the course of treatment for infertility, or else during the first trimester of pregnancy or at the start of the second trimester.

Other recommendations concern specifically couples when the woman is pregnant: before meeting the clinician: i.e. sending an explanatory pamphlet to the patient’s home before the appointment so as to encourage an independent viewpoint; if both members of the couple accept screening then preferably provide counselling to them both simultaneously; get the couple to sign consent to, or refusal of (!) screening; whereas willing couples belonging to low risk ethnic groups would only need to sign for consent.

At the end of 2003, it would seem that antenatal screening is very frequent in the United States (Vallance, Ford, 2003). Several HMOs have included the procedure in the prenatal care systematically offered to their members. The Canadian Association of Obstetricians and Gynaecologists, on the contrary, does not recommend a generalisation of this approach.

United Kingdom

Evolution of thinking in the United Kingdom was influenced by experience accumulated in the 90s in Scotland, where several pilot tests were held (Brock, 1995, 1996 ; Mennie *et al.*, 1993). Other doctors came to be persuaded that this preventive approach could be useful (Cuckle, 1996; Mennie, 1997).

In 1999, recommendations in favour of generalising antenatal screening were published by a group that advises the government on all matters of policy regarding screening (Murray *et al.*, 1999). However, in 2001, the National Screening Committee, another official body, decided against the advisability of implementing a national prenatal screening programme, because of the small number of mutations under scrutiny and the lack of data regarding the clinical severity of the disorder that could serve as a basis to facilitate informed consent. The offer to extend neonatal screening to a larger number of new borns than the 18% who were screened in 2001 was also rejected, because of uncertainties regarding benefits, divergent opinions about protocols, lack of consensus on what care should be given to children with low-grade symptoms, and the absence of quality management structures beyond the local level.

At present, it seems that the National Screening Committee has changed its mind, although why it has done so is not clear. A working group meeting in December 2002 pronounced itself in favour of antenatal screening for couples. They proposed that a small number of pilot tests be organised along the Scottish model. The group also wanted to neonatal screening programme to be continued. The Committee intends to review the situation before April 2004 and it is very likely that antenatal screening will be organised in the coming months (Peckham, 2003).

What is the French position?

A recent review of the literature under the aegis of INSERM by specialists in the various disciplines involved in antenatal diagnosis (Dommergues... 2003) contains two

comments regarding antenatal screening for cystic fibrosis that are germane to our presentation:

1. *“Screening of heterozygotes should be offered in the antenatal phase to all women in populations where prevalence is high, and the offer should be combined with a balanced set of data on the disease, the test, and its consequences. If screening is performed, it must be done as early as possible in pregnancy so that couples can take any decision of concern to them in a climate of serenity”.*
2. *“The prevalence threshold at which such screening should be proposed is however a problem, and at the present time in France, population screening of heterozygotes is not recommended”.*

Two issues remain open

1. Is it likely that antenatal screening for cystic fibrosis will be opening the way to screening for other recessive disorders by molecular analysis techniques? An American specialist (Grody, 1999) commented that, although a certain number of delicate issues had not yet been solved, there was no doubt that population screening for cystic fibrosis carriers using molecular genetic methods would soon become very familiar, and would probably produce an unprecedented volume of testing for a single disease among all the molecular pathologies. It would therefore serve as a precursor of the results that other molecular test programmes would contribute as and when the Human Genome project continued to elucidate more and more genes causing disease. The success or failure of the cystic fibrosis programme would probably have an impact on public acceptance of future programmes. It was obvious that genetic testing for cystic fibrosis mutations had been extremely beneficial for at-risk couples and the families of patients. What remained to be seen was whether it would also be beneficial to the population as a whole.

2. What is the aim of antenatal screening for cystic fibrosis? Most authors state that it must serve to reinforce parental competence for making an informed decision during pregnancy. Few of them express themselves like Murray and colleagues who state: *“The aim of genetic screening for CF is to reduce the birth prevalence of the disorder. This is principally achieved by identifying carrier couples who can have prenatal diagnosis and selective termination of pregnancy »*. Other authors wonder whether displacement of preventive intentions of families with an affected child to the general population does not stem from an implicitly eugenic desire to eradicate the disease. Economic studies (cost/benefit or cost/effectiveness¹¹) produce divergent results (Rowley, 1998). But it does seem to be accepted that antenatal screening is a saving for public health systems if it addresses high risk groups (Vintzileos, 1998), if participation is high (Farrell, Fost, 2002), and if couples use the information provided for more than one pregnancy (Asch, 1998).

¹¹ Cost/benefit studies compare the cost of the screening procedure to savings made because of not having to provide medical and social care to the patient ; cost/effectiveness studies compare the cost of the procedure with savings achieved by termination of an affected foetus (cf. Rowley, Loader, Kaplan, 1998).

Bibliography

American College of Obstetricians and Gynecologists (1991), *Current status of cystic fibrosis carrier screening*. ACOG committee opinion no. 101. Washington DC : American College of Obstetricians and Gynecologists.

American College of Obstetricians and Gynecologists, American College of Medical Genetics (2001), *Preconception and Prenatal Carrier Screening for Cystic Fibrosis, Clinical and Laboratory Guidelines*, 31 p.

Asch D.A. et al. (1996), "Genetic screening for reproductive planning : methodologic and conceptual issues in policy analysis", *Am J Public Health*, 86 : 684-90.

Asch D.A. et al. (1998), "Carrier screening for cystic fibrosis : costs and clinical outcomes", *Med Decis Making*, 18, 2 : 202-12.

Bekker H. et al. (1994), "The impact of population based screening for carriers of cystic fibrosis", *J Med Genet*, 31, 5 : 364-8.

Brock D.J. (1995), "Heterozygote screening for cystic fibrosis", *Eur J Human Genet*, 3, 1 : 2-13.

Brock D.J. (1996), "Prenatal screening for cystic fibrosis : 5 years' experience reviewed", *Lancet*, 347, 8995 : 148-50.

Clausen H. et al. (1996), "Psychological and social impact of carrier screening for cystic fibrosis among pregnant woman (sic.) – a pilot study", *Clin Genet*, 49 : 200-5.

Cuckle H.S. et al. (1995), « Cost effectiveness of antenatal screening for cystic fibrosis », *BMJ*, 311 : 1460-1464.

Danish Council of Ethics (1993), *Ethics and mapping of the human genome, Genetic screening*.

Delvaux I. et al. (2001), "Carrier screening for cystic fibrosis in a prenatal setting", *Genet Test*, 5, 2 : 117-25.

Dierickx K (2003), « Dépistage génétique : y a-t-il un consentement éclairé ? » *Laennec*, 1 : 7-20.

Dommergues M., Aymé S., Janiaud P., Séror V. (dir.), *Diagnostic prénatal, pratiques et enjeux*, INSERM (Questions en santé publique), 574 p.

Farrell P.M., Fost N. (2002), "Prenatal screening for cystic fibrosis : Where are we now ?" *J.Pediatr.* 141: 758-63.

Grody W.W. (1999), "Cystic Fibrosis, Molecular Diagnosis, Population Screening, and Public Policy", *Arch Pathol Lab Med*, 123 : 1041-6.

Henneman L., Poppelaars F.A., ten Kate L.P. (2002), "Evaluation of cystic fibrosis carrier screening programs according to genetic screening criteria", *Genet Med*, 4, 4 : 241-9.

Henneman L. et al. (2002), "Preconception cystic fibrosis carrier couple screening : impact, understanding, and satisfaction", *Genet Test*, 6,3 : 195-202.

Henneman L. et al. (2003), "Offering preconceptional cystic fibrosis carrier couple screening in the absence of established preconceptional care services", *Community Genet*, 6, 1 : 5-13.

Jung U. et al. (1994), "Acceptability of carrier screening for cystic fibrosis during pregnancy in a German population", *Hum Genet*, 94 : 19-24.

Levenkron J.C., Loader S., Rowley P.T. (1997), "Carrier Screening for Cystic Fibrosis : Test Acceptance and One Year Follow-Up", *Am J Med Genet*, 73 : 378-86.

Loeben G.L., Marteau T.M., Wilfond B.S. (1998), "Mixed messages : presentation of information in cystic fibrosis screening pamphlets", *Am J Hum Genet*, 63, 4 : 1181-9.

Mennuti M.T., Thomson E., Press N. (1999), "Screening for cystic fibrosis carrier state", *Obstetrics & Gynecology*, 93, 3: 456-461.

Mitchell J. et al. (1993), "What young people think and do when the option for cystic fibrosis carrier testing is available", *J Med Genet*, 30, 7 : 538-42.

Murray J. et al., (1999), "Screening for cystic fibrosis", *Health Technology Assessment*, 3,8 (Executive Summary), 5 p.

National Institutes of Health, "Genetic testing for cystic fibrosis . National Institutes of Health Consensus Development Conference Statement on genetic testing for cystic fibrosis", *Arch Intern Med*, 1999 ; 159, 14 : 1529-39.

National Screening Committee, Antenatal Sub-Group (2002), *Antenatal screening for cystic fibrosis : Workshop*, 4 p.

Nielsen R., Gyrd-Hansen D. (2002), "Prenatal screening for cystic fibrosis : an economic analysis", *Health Econ.* 11, 4 : 285-99.

Peckham, C., Communication orale, 2003.

Poppelaars F.A. et al. (2003), "Possibilities and barriers in the implementation of a preconceptional screening programme for cystic fibrosis carriers : a focus group study", *Public Health*, 117, 6 : 396-403.

Rowley P.T., Loader S., Kamlan R.M. (1998), "Prenatal Screening for Cystic Fibrosis Carriers : An Economic Evaluation", *Am J Human Genet*, 63 : 1160-74.

Schmidtke J. (1998), "A Commentary on the NIH Consensus Development Statement 'Genetic Testing for Cystic Fibrosis'", *Community Genetics*, 1 : 53-6.

Scotet V. *et al.* (2000), "Neonatal screening for cystic fibrosis in Brittany, France : assessment of 10 years' experience and impact on prenatal diagnosis", *Lancet*, 356, 9232 : 789-94.

"Statement from the National Institutes of Health Workshop on Population Screening for the Cystic Fibrosis Gene", *N Engl J Med* 1990 ; 323 : 70-1.

"Statement of the American Society of Human Genetics on cystic fibrosis carrier screening", *Am J Human Gen* 1992 ; 51 : 1443-4.

Vallance H., Ford J. (2003), "Carrier Testing for Autosomal-Recessive Disorders", *Critical Reviews in Clinical Laboratory Sciences*, 40, 4 : 473-97.

Vintzileos A.M. *et al.* (1998), "A Cost-Effectiveness Analysis of Prenatal Carrier Screening for Cystic Fibrosis", *Obstetrics & Gynecology*, 91, 4 : 529-34.

Wagener J.S., Sontag M.K., Accurso F.J. (2003), "Newborn screening for cystic fibrosis", *Curr Opin Pediatr*, 15, 3 : 309-15.

Wildhagen M.F., ten Kate L.P., Habbema J. (1998), "Screening for cystic fibrosis and its evaluation", *Br Med Bull*, 54, 4 : 857-75.

Wilson R.D. *et al.* (2002), « Cystic fibrosis carrier testing in pregnancy in Canada », *J Obstet Gynaecol Can*, 24, 8 : 644-51.

Witt D., *et al.* (1996), « Cystic fibrosis heterozygote screening in 5, 161 pregnant women », *Am J Hum Genet*, 58, 4 : 823-35.

Witt D. *et al.* (2003), "Cystic fibrosis prenatal screening of over 50 000 members in a large HMO/ Program update with an emphasis on the outcomes of high-risk pregnancies, reduction in the incidence of CF, and clinical utility », Abstract, Annual Meeting of the American Society of Human Genetics, 2003.

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