Review article

Cystic fibrosis screening and community genetics

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Cystic fibrosis (CF), the commonest serious recessively inherited disease of Caucasians, is fast becoming preventable. The gene in which mutation can lead to CF, the cystic fibrosis transmembrane conductance regulator (CFTR), has recently been identified, and a deletion of three DNA base pairs that removes a phenylalanine residue from position 508 of the protein product accounts for 60 to 80% of CF mutations in the UK population.¹ This mutation can be detected by relatively simple DNA methods.^{2,3} Consequently, geneticists are now confronting an imminent need to set up population screening for CF carriers, a challenge that, if appropriately seized, could greatly improve the delivery of genetics services as a whole.

At present, clinical geneticists are mainly concerned with diagnosis, counselling, and prenatal diagnosis for families referred to them. Relatively few have yet been drawn into the issues of population screening and the outreach approach to the community that it entails. However, a recent report of the Royal College of Physicians (RCP)⁴ pointed out the existence of a range of 'community genetics services', that is, preventive genetics services based on population screening that are often delivered by obstetricians and others, rather than by clinical geneticists. They include (1) neonatal screening for phenylketonuria, congenital hypothyroidism, and other disorders; (2) screening in pregnancy for rhesus blood group and viral infections, maternal serum AFP screening, the offer of fetal karyotyping to older women, and midtrimester ultrasound scanning for fetal anomalies; (3) population screening for carriers of haemoglobin disorders or Tay-Sachs disease.

The RCP report noted many shortcomings in the delivery of these services and proposed that they

should be improved, not only by increased resource allocation but also by appropriate regional and national organisation, public education and professional training, and service monitoring. Increased involvement of clinical geneticists in delivery of community genetics services was strongly recommended, especially with regard to organisation, monitoring, information, and counselling. The new developments in CF are likely to bring this about, since clinical geneticists will necessarily play a prominent part in organising national screening, because of the large numbers and the DNA technology involved. The time has come to plan a comprehensive prevention programme for CF, based on a national policy and including laboratory services, infrastructure for screening, information for the public, education for health professionals, prenatal diagnosis, and service monitoring.

Carrier screening and prenatal diagnosis for recessively inherited disorders

In dominant or X linked conditions, such as Huntington's chorea or haemophilia, the family history is the key to identifying carriers, but with recessively inherited conditions, like cystic fibrosis or the haemoglobin disorders, the issues of carrier screening are very different.

(1) The number of carriers vastly exceeds the number of affected children: about a hundred times more CF carriers than patients are born annually. When carrier screening is possible and desirable, the large numbers imply that screening and counselling must be integrated into primary health care.

(2) Most affected infants are born to couples without a family history. Population screening, when it is possible, is the only way to detect most carriers. Few of the carriers so detected will be familiar with the major disease.

(3) When prenatal diagnosis is possible but carriers cannot be detected, only the second affected birth to the same couple can be avoided. For the past few years, this has been the situation with CF. Though such 'retrospective' prevention is very beneficial for

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families, it makes relatively little difference to the incidence of the disease.

(4) The possibility of detecting carriers transforms what can be done in practical terms, because carrier couples could be identified 'prospectively', that is, before they have any children so, in principle, prenatal diagnosis could be offered in every pregnancy.

When screening and counselling are delivered efficiently and equitably, the birth incidence of affected infants comes to reflect the informed choices of couples at risk. Diseases that are considered thoroughly undesirable, like thalassaemia or Tay-Sachs disease, may be all but eradicated,⁵ but the fall in birth rate will be proportionately less with diseases that are perceived as less severe, like sickle cell disease or phenylketonuria. We do not yet know where on this scale cystic fibrosis stands.

The immediate question is, how acceptable is prenatal diagnosis for CF to the families at risk? Some paediatricians looking after affected children remark on a low uptake rate among the families. Some geneticists have the impression that about 70% of at risk couples request prenatal diagnosis, and an attitude survey among the general public in London suggested even higher potential uptake.⁶ Clearly there is a significant demand for prenatal diagnosis and population screening will be necessary to allow an informed choice. However, this will call for funding and many people, including Health Administrators, will have to be persuaded that it is necessary. Objective figures based on experience are required to show the need for screening, and an analysis of non-financial as well as financial costs and benefits is also necessary.⁴

When an inherited disease becomes preventable through carrier screening, it has been recommended to carry out studies in families detected retrospectively (with an affected child) as a first step, in order to assess acceptability, verify methodology, and identify problems among couples who are already well aware of the problem.⁷ In reality, the first stage has already been passed for cystic fibrosis, but as the results have not been systematically collected, we still lack the objective statistical information we need.

The acceptability of prenatal diagnosis is influenced by the accuracy, timing, and obstetric risk of the procedure as well as by the severity of the disorder. Prenatal diagnosis of CF was first achieved by assay of amniotic fluid enzymes at 18 to 20 weeks' gestation, with about a 5% false positive and false negative rate.⁸ The development of DNA methods based on linkage with restriction fragment length polymorphisms (RFLPs)⁹ introduced definitive carrier diagnosis, and moved prenatal diagnosis for CF back to the first trimester and increased its accuracy. However, some diagnoses still had to be confirmed by enzyme assay in the second trimester, and the obstetric risk of

chorionic villus sampling was unknown.¹⁰ As further linkages were established with even closer RFLPs¹¹ and the commonest mutation has been defined, reliable diagnosis has become possible for more and more families. In the meantime, the risk of CVS has been shown to be acceptably low.¹² As laboratory and obstetric methods have improved, the acceptability of prenatal diagnosis for CF is likely to have increased over the past five years.

We now urgently need to know the number of couples with affected children who have undertaken pregnancies since prenatal diagnosis became possible, the number that requested prenatal diagnosis, the method used, and the outcome. Experience of the haemoglobin disorders suggests that the behaviour of couples with affected children is a reasonable predictor of the behaviour of couples detected prospectively.⁷

Lessons from the Mediterranean experience with thalassaemia

Screening will be required for the equivalent of at least one birth cohort of the population per year, but the real requirement will be at least twice as high because it will be necessary to promote several approaches to screening, and many relatives of the identified carriers will also wish to be screened. With about 700 000 births a year, the annual requirement in the UK will be for at least 1.5 to 2 million screening tests; about 70 000 carriers will be detected and require full information; and up to 1500 couples at risk will require counselling and the option of prenatal diagnosis. Such a large service will require careful planning.

Fortunately, the thalassaemia control programmes of southern Europe provide a provisional blueprint for developing a screening service for a common and serious recessively inherited disease. The Italian experience reported by the WHO¹³ provides the best model for the UK, because the populations of the two countries are similar in size and the birth incidence of thalassaemia major in Italy is similar to that of CF in the UK. The outstanding lessons are as follows.

(1) A screening programme is best organised on a regional basis. It requires the support of the Regional Health Authority. In the UK this means that a very good case will have to be presented, including cost-benefit analysis and organisation of a monitoring system.

(2) A regional 'management group' including representatives of all the medical services involved, public health officials, and lay support associations is required. Support associations have a vitally important role in voicing the community's need for the service, in winning the support of the health authorities, and in informing the public.

(3) Reliable and adequate local services for carrier screening must be set up, and a quality control system is essential.

(4) Diagnostic facilities form only a small part of the whole service. A substantial infrastructure (discussed below) is required to deliver screening.

(5) Information and screening are two different activities. Information should be provided wherever and whenever possible. In many regions of Italy it is included in the primary school curriculum; in Lombardy couples planning to marry are given a booklet about avoidable reproductive risks by the Registrar of Marriages; obstetricians are expected to inform women during pregnancy; and thalassaemia receives considerable attention in the media.

(6) The choice of screening strategy is less simple. There is no single 'right' approach and a number of complementary strategies may be needed. It is necessary to start with what is possible. As more and more carriers are diagnosed and counselled, community involvement, understanding, and support increase, and the strategy is likely to evolve.

(7) Genetic population screening can be carried out adequately only if primary care workers are involved. However, it can be considerably more difficult to inform the medical profession and ensure their cooperation than it is to inform the public. A specific, well designed programme appealing to primary care workers is necessary.

(8) Though doctors may consider the heterozygous state to be quite trivial, carriers themselves consider it exceedingly important, particularly as they may hand it on to their children. They require complete information.

(9) The need for face to face counselling of single carriers is inversely proportional to the level of information among the community. However, couples at risk always require intensive counselling by an expert.

(10) Public attitudes towards screening evolve. For example, carriers very rarely use knowledge of their carrier status in selecting a partner,¹⁴ but it takes some years of experience for people in general to understand that they should not be expected to do so.

(11) The delivery of services, both for patient care and for prevention, must be monitored. This can be done simply through a regional and national patient register updated annually.

Many of the general issues of genetic screening, including the need for a regional organisation, education, counselling, professional training, and monitoring, are covered in the RCP report. Here it seems appropriate to concentrate on the nature of the infrastructure that will be needed.

The infrastructure for screening

It will be necessary to provide: (1) information to the population; (2) a system for collecting samples from a cohort of the population at some point before reproduction and delivering them to a laboratory; (3) a

network of diagnostic laboratories with a quality control system; (4) a system for reporting the results to doctors and the people concerned; (5) an information storage and retrieval system; (6) information and counselling for carriers; (7) adequate expert centres for counselling couples at risk and providing prenatal diagnosis; and (8) a system for monitoring the service.

We are a long way from being able to meet these requirements. Some pilot projects should be started immediately to work out how an infrastructure can best be developed. Various systems can be envisaged. Screening might be offered to young people in schools, premaritally, as part of a service provided by GPs, in family planning clinics, in antenatal clinics, or by newborn screening.

Premarital testing is a disappearing target, as formal marriage is going out of fashion in much of Europe. Where it is the policy (in Greece and parts of Italy), most couples come for testing only when the woman is pregnant. Screening in high schools, offered for Tay-Sachs disease in Montreal¹⁵ and for thalassaemia in Latium in Italy,¹⁶ may be a good strategy but it requires a well informed population and a developed infrastructure, and there is a long interval between testing and the use of the information.

It is only in the antenatal and newborn periods, pregnant women and newborn babies being 'captive' populations, that anything resembling the infrastructure necessary for screening yet exists. For practical reasons, it will be necessary to start CF screening at one of these two points.

What should be done now? There is no question that the new findings should be used at once for carrier and prenatal diagnosis for families detected retrospectively, and this is already under way. But should screening be started now and, if so, what strategy should be used?

Neonatal screening for CF using DNA methods would identify both affected and carrier infants, and the aim would be to follow up the parents of the latter to identify couples at risk. However, neonatal screening is a very inefficient way to identify couples at risk, because 50% will be missed: 25% will already have had an affected baby (and may not be happy when they realise this could have been avoided had screening been provided antenatally) and 25% will have a normal baby and so remain undetected. Neonatal screening seems quite unrealistic as an approach for identifying couples for reproductive counselling.

The idea of newborn screening seems attractive because screening for phenylketonuria and congenital hypothyroidism is already taking place. However, this service aims only to identify and refer relatively few infants with potentially serious conditions. Little if any information is given to parents, and there is no special provision for counselling. It is an illusion to think that neonatal screening for CF carriers could be set up simply because there is a system for collecting

samples and analysing them in a laboratory. The experience of sickle cell disease shows clearly that it is better not to inform families at all than to try to inform them without adequate counselling.¹⁷ Four to five percent of all families would need counselling about the trait detected in their infant at an emotionally sensitive time, and there is a risk of awkward findings such as non-paternity. The necessary manpower simply is not available. It will become available only when primary care workers are fully involved in delivering the service.

Antenatal carrier screening involves screening pregnant women at the time of antenatal booking, and then offering testing to the partners of carriers, as is done for the haemoglobin disorders at present. Most couples at risk are identified in time for the offer of prenatal diagnosis, and some counselling for reproductive risks is already established in antenatal practice, however imperfectly. Probably the most important limitation is that women who present at the antenatal clinic after the 11th week of pregnancy would miss the option of prenatal diagnosis in the first trimester. This problem might be overcome, but antenatal screening definitely has too many other disadvantages to be selected as the only approach.⁴ However, any other net, such as screening in primary care or in schools, is likely to be 'leaky', so antenatal screening will always be needed as a back up strategy.

The question of whether screening should be offered to pregnant women now, when only 80% of carriers can be detected, is probably academic, since the main remaining CF mutations will soon be identified. However, it is worth remarking that the basic requirements for screening (namely clear diagnosis, clear information, and effective avoiding action¹⁸) are not fulfilled when only 80% of carriers are identified. About 4% of pregnant women would have a positive result, but it would not be possible to exclude CF carrier status in their partners, and this could generate an unacceptable level of anxiety. Nevertheless, it is reasonable to plan pilot studies among pregnant women in the near future when this problem has been overcome.

It is acceptable to set up pilot studies immediately, aimed at people of reproductive age who have not yet had children. This could best be done from primary care, especially as recent changes in organisation of primary care favour more emphasis on prevention. This could well prove to be the best approach, but screening for carriers of CF or haemoglobin disorders will be delivered at this level only if it is perceived as part of a larger, comprehensive package of community genetics services, as summarised in the RCP report.⁴ Women actually planning a pregnancy can often be identified in family planning clinics (the majority of which are now run by primary care teams) and could be offered pre-pregnancy screening and counselling. This approach would reach only a fraction of the

group at risk, and in common with antenatal screening tends to perpetuate the idea that only women are concerned with genetic and reproductive problems. A complementary approach is to offer screening to everyone of reproductive age registered with a practice.

To introduce such a package of screening into primary care will require a great deal of organisation, time, and money. It must be decided exactly what genetics primary care workers need to know, and a module must be introduced into the medical and nursing curricula. Refresher courses must be organised for general practitioners, health visitors, and nurses. Educational materials such as posters, booklets, and videotapes must be designed, produced, and made available for general practitioners' surgeries. Experience must be gained and decisions made about which member of the primary care team will be responsible for basic information and counselling for carriers; this could well be a health visitor or nurse. Clear guidance must be given on the limits of genetic counselling in primary care and when and to whom to refer. A network of specially trained genetic counsellors, based at genetics or other expert centres, must be available to counsel all the couples at risk for CF or other conditions who are referred from primary care.

The establishment of the necessary infrastructure for genetic screening based in primary care will improve the delivery of medical genetics services to the whole population, and will lay a foundation for other forms of genetic screening, such as screening for genetic risk factors for common diseases, in the future.

- 1 Riordan J, Rommens JM, Kerem BS, *et al.* Identification of the cystic fibrosis gene: cloning and characterisation of complementary DNA. *Science* 1989;245:1066-71.
- 2 Newton CR, Heppinstall LE, Summers C, *et al.* Amplification refractory mutation system for prenatal diagnosis and carrier assessment in cystic fibrosis. *Lancet* 1989;ii:1481-3.
- 3 Ballabio A, Gibbs RA, Caskey CT. PCR test for cystic fibrosis deletion. *Nature* 1990;343:220.
- 4 Prenatal diagnosis and genetic screening: community and service implications. *A report of the Royal College of Physicians, September 1989.* London: The Royal College of Physicians, 1989.
- 5 Angastiniotis MA, Hadjiminis MG. Prevention of thalassaemia in Cyprus. *Lancet* 1981;i:369-70.
- 6 Watson E, Williamson R, Chapple J. Cystic fibrosis carrier screening: a community survey. *J R Coll Gen Pract* (in press).
- 7 Community control of hereditary anaemias. Memorandum from a WHO meeting. *Bull WHO* 1983;61:63-80.
- 8 Brock DJH. Prenatal diagnosis. In: Goodfellow P, ed. *Cystic fibrosis*. Oxford: Oxford University Press, 1989:66-91.
- 9 Beaudet A, Bowcock A, Buchwald M, *et al.* Linkage of cystic fibrosis to two tightly-linked DNA markers: joint report from a collaborative study. *Am J Hum Genet* 1986;39:681-93.
- 10 Modell B. Chorionic villus sampling: evaluating safety and efficacy. *Lancet* 1985;i:737-40.
- 11 Beaudet AL, Feldman GL, Fernbach SD, Buffone GJ, O'Brien WE. Linkage disequilibrium, cystic fibrosis and genetic counseling. *Am J Hum Genet* 1989;44:319-26.
- 12 Canadian Collaborative CVS-Amniocentesis Clinical Trial Group. Multicentre randomised clinical trial of chorion villus sampling and amniocentesis. First report. *Lancet* 1989;i:1-6.
- 13 The haemoglobinopathies in Europe. Report of two meetings of the WHO European/Mediterranean Working group on haemoglobinopathies. WHO Regional Office for Europe, offset publication IPC/MCH 110. (May be obtained free of charge

- from: Maternal and Child Health Division, WHO Regional Office for Europe, 8 Scherfigsvej, DK-2100 Copenhagen, Denmark.)
- 14 Angastiniotis MA, Kyriakidou S, Hadjiminis M. How thalassaemia was controlled in Cyprus. *World Health Forum* 1986;7:291-7.
 - 15 Clow CL, Scriver CR. Knowledge about and attitudes towards genetic screening among high-school students: the Tay-Sachs experience. *Pediatrics* 1977;59:86-91.
 - 16 Bianco I, Graziani B, Lerone M, *et al.* A screening programme for the prospective prevention of Mediterranean anaemia in Latium: results of seven years' work. *J Med Genet* 1984;21:268-71.
 - 17 Beutler E, Boggs DR, Heller P, Maurer A, Motulsky AG, Sheehy TW. Hazards of indiscriminate screening for sickle cell disease. *N Engl J Med* 1971;285:1485-6.
 - 18 Cuckle HS, Wald NJ. Principles of screening. In: Wald NJ, ed. *Antenatal and neonatal screening*. Oxford: Oxford University Press, 1984.