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Active cascade testing for carriers of cystic fibrosis gene

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Abstract

***Objective*—To examine the acceptability, practicability, efficiency, and application of active screening for carriers of the cystic fibrosis gene in the extended families of those in whom the disease is present (cascade screening).**

***Design*—Paediatricians and physicians provide details of their affected patients, pedigrees are drawn up, and relatives offered tests after initial contact by the affected nuclear families. Affected patients are genotyped in a laboratory with a special interest in the genetics of cystic fibrosis.**

***Setting*—North Western health region.**

***Subjects*—Relatives and partners of 607 people with cystic fibrosis.**

***Interventions*—Genetic counselling by letter for people found to be carriers; formal genetic counselling and when indicated arrangements for prenatal diagnosis for couples discovered to be carriers.**

***Main outcome measures*—Number of carrier couples detected; action in pregnancy of detected carrier couples; extent of the uptake of screening by relatives.**

***Results*—Of 1563 relatives or partners tested, 15 carrier couples were detected; of nine pregnancies undertaken by these 15, eight had prenatal tests and three terminated pregnancies. An average of 16 people per family have come forward for testing so far.**

***Conclusions*—Cascade screening for carriers of cystic fibrosis is well accepted by relatives, especially on the mother's side of the family; it is 10 times more efficient in detecting carrier couples than unfocused screening. Detected carrier couples make practical use of the information in pregnancy. Active cascade screening for carriers is effective in cystic fibrosis and widespread application is recommended. These principles could be applied to other recessive disorders.**

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Introduction

As long as cystic fibrosis remains a disorder with considerable morbidity and reduced lifespan there will be those who will want to avoid having affected offspring. Carrier screening allows the discovery of couples at one in four risk of having children affected by this autosomal recessive disorder. Since 1989 when the gene and its major mutation, ΔF508, were discovered[1] testing capable of detecting 80% to 90% of carriers has been feasible, especially in countries such as Britain, where ΔF508 accounts for a high proportion of all cystic fibrosis mutations.[2]

There is more to introducing screening than simply tests capable of detecting carriers. As soon as the gene was discovered it was generally agreed that carrier testing should be offered to those with a family history of cystic fibrosis, whereas general or unfocused population screening required careful study to determine whether and how it might be introduced.[3] Several official and quasiofficial bodies took no set position about whether screening should be offered to the general population but did recommend screening for those with a family history.[4,5] After the publication of results of pilot studies of general population screening on pregnant and non-pregnant populations[6-8] doubts still remain about whether the time is now ripe for general screening.[9] Some added stress was noted, at least in the short term, in women or couples offered screening in pregnancy, though participation was fairly high.[10] Screening offered in general practice to a non-pregnant population had a poor uptake unless the tests were taken on the day of the visit to the general practitioner by a keen research worker.[7]

Some profession led general screening programmes[6,10,11] currently exist, being aimed at women or couples with pregnancies under way. The idea is to use the "turnstile" of pregnancy as the way to detect couples at risk. Thus with relatively high uptake in a group of people who would find it more difficult to refuse a test once offered than would people who were not pregnant, the hope is to identify a great number of carrier couples and to offer them prenatal diagnosis and selective abortion. In two programmes a way of dealing with the stress of testing in pregnancy has been to inform only those couples in which both people had positive results and therefore were at one in four risk of having affected offspring.[6,10] It is accepted that were

individual people told that they were carriers this would have major counselling implications, as one in 25 people are carriers. Thus such programmes are pragmatic and necessarily paternalistic in that individual people are not informed of their carrier status when their partners are negative.

Since most women report their pregnancies to their general practitioner early pregnancy screening can be based in general practice.[12] The programme of Harris *et al* offers couples screening in early pregnancy, in time to offer chorionic biopsy to carrier couples.[11] It takes account of the real risk of stress in the pregnancy. While providing results to all those tested it arranges for support with the help of the regional genetics department, which is linked to the project. For those whose test results are positive the decision about whether to suggest tests to relatives is left to their discretion.

Although there was general agreement that carrier testing of relatives should be implemented, no one promoted it actively. Knowing of the interest shown by some relatives we decided on an active programme, believing that there were many more relatives who would be interested in being tested than had come forward unprompted. We expected a far greater yield of carrier couples than in unfocused screening simply because of the greatly increased risk of being a carrier in the relatives of affected people. We also expected there to be a better basic understanding and desire to know results and perhaps act on them than in people with no previous or personal knowledge of cystic fibrosis. We hoped to offer most of our testing to non-pregnant family members, the family history and our active approach providing the impetus for testing which does not seem to be present otherwise in people not directly affected by pregnancy. By and large our expectations have proved correct. While the public's knowledge is rising to the point when there might be a consumer led demand for general carrier screening, either before or in early pregnancy, active cascade testing is worth implementing on a wide scale.

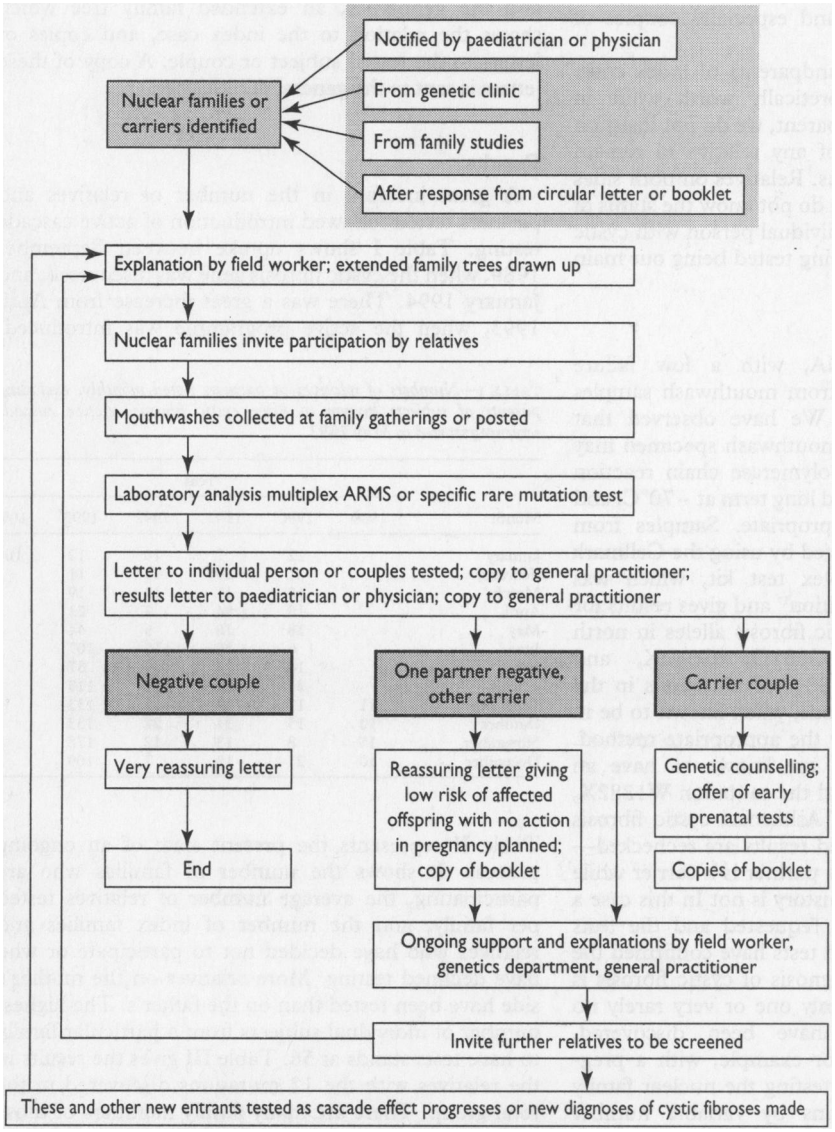

FIG 1—*Flow chart of cascade screening programme for carriers of cystic fibrosis*

The paediatric genetics unit at this hospital has a longstanding interest in many aspects of cystic fibrosis, including care of affected patients, genetic counselling, and analysis of the genotypes of a large number of affected subjects from north west England. Since 1984 we have been storing DNA from patients with cystic fibrosis, and a large bank has built up over the years. Soon after the discovery of the cystic fibrosis gene, the bank was analysed for ΔF508,[13] which was found to account for 81% of cystic fibrosis genes in north west England. To date, 27 mutations have been detected in our population, eight of them having been discovered for the first time in our laboratory. These have all been reported to the International Cystic Fibrosis Genetic Analysis Consortium. A total of 1254 chromosomes have been analysed, and the number of mutations detected in our population has risen to 93% from the 92% reported previously.[2] This genetic knowledge has been put to various uses, including genetic counselling of the families of patients tested.[14] Now we are extending this to the relatives.

Since 1989 our laboratory genotype reports have indicated that we would be pleased to test and counsel any relatives who wished this. Though those contacted were enthusiastic, general uptake was modest. From April 1993 a programme of active cascade testing for carriers has been operating with dedicated staff working with the infrastructure support of the clinical genetics unit, the DNA laboratory, and cystic fibrosis clinics. Our approach is to advertise and promote screening for carriers in known families in a cascade fashion, moving out from the index case by testing the relatives of all those found to be carriers.[15] Thus eventually we shall reach a considerable proportion of those at high risk of having affected offspring and shall provide increased reassurance to all those whose risk after testing is low.

Subjects and methods

The North Western Regional Health Authority agreed funding in 1992 for a programme of cascade screening for cystic fibrosis as a regional development with the support of the regional genetics committee. Funding from April 1993 was authorised and a dedicated fieldworker (TR), molecular geneticist (AH), and clerk (GD) were appointed. Early in 1993 all paediatricians and physicians in the region were contacted, told of the scheme, and invited to inform their families with cystic fibrosis and to take part by providing names and addresses of their patients with cystic fibrosis. A total of 537 names of living patients, excluding affected siblings, were provided; many of them were already known to us from our genotyping over the past years. We also had available the names of a further 70 people who had died.

An explanatory booklet was prepared for use by families with affected members and their relatives. The flow diagram (fig 1) shows the nucleus of the programme in the genetics department with the bank of known genotypes and then the involvement and interaction of the families, the fieldworker, the laboratory, genetic counselling service, general practitioner, and clinical specialist.

Index families with affected members are contacted by the fieldworker, often at visits to cystic fibrosis clinics, and arrangements are made to draw up formal family trees. Genotyping is completed on those subjects with cystic fibrosis not previously tested and on their parents. Families are given copies of the booklet and invited to contact relatives with the offer of testing by mouthwash. A wish to participate is notified either through the index patient's family or by the relative contacting the dedicated departmental telephone number or address given in the booklet. Most testing is on mouthwash specimens, either collected or sent through the post. All those tested receive a written report stating whether they are carriers or what their residual risk is after testing. As only 88% of cystic fibrosis mutations are tested for, people with negative results have their carrier risk reduced; we cannot say that they are not carriers (except in the case of siblings of people with cystic fibrosis). Couples are given their combined risk of having affected offspring. The booklet explains how the risks are calculated. All those found to be carriers are invited to inform their relatives and to invite them to request testing, hence the term cascade. Unless we are asked specifically not to, a copy of the report is sent to the person's general practitioner. By and large children are not tested. An exception is when a sibling has cystic fibrosis and we want to exclude the condition. The large number of index families notified has necessitated sending letters to those not yet visited for family trees inviting them to notify their relatives of childbearing age of the scheme and inviting their participation. Cascade screening is targeted mainly at people and especially couples of childbearing age.

Though testing of the grandparents of index cases with cystic fibrosis is theoretically worth while in identifying the carrier grandparent, we do not insist on this and respect the wish of any relative to remain ignorant of their carrier status. Relatives on both sides are offered testing, even if we do not know the status of the relatives who link the individual person with cystic fibrosis, interest shown in being tested being our main guiding criterion.

LABORATORY ASPECTS

Ample amounts of DNA, with a low failure rate, have been obtainable from mouthwash samples collected in 4% sucrose.[16] We have observed that chocolate and apple in the mouthwash specimen may interfere with subsequent polymerase chain reaction tests. DNA samples are stored long term at −70°C, and an aliquot is tested as appropriate. Samples from relatives and partners are tested by using the Cellmark Diagnostics ARMS Multiplex test kit, which was developed with our collaboration[17] and gives results for the four most common cystic fibrosis alleles in north west England (ΔF508, G551D, G542X, and 621+1(G>T)) and covers 88% of mutations in the region. Specific rarer mutations, when known to be in the family, are tested for by the appropriate method. In addition, when subjects are known to have an Ashkenazi Jewish background the mutation W1282X, which accounts for 60% of Ashkenazi cystic fibrosis genes, is tested.[18] Unexpected results are rechecked—for example, discovery that a partner is a carrier while the relative with the family history is not In this case a second set of specimens is requested and the tests repeated. (So far all repeated tests have confirmed the original result.) When a diagnosis of cystic fibrosis is firm in an index case but only one or very rarely no cystic fibrosis mutations have been discovered, analysis has on occasion (for example, with a pregnancy under way) included testing the nuclear family for intragenic polymorphisms by variable number dinucleotide repeat (VNDR)[19] to identify the cystic fibrosis bearing chromosome which can then be tested for in the relative needing to know his or her carrier status.

Origins of carrier testing cascades
(with file abbreviations shown)

- Index cases (C) and their relatives (CSF)—cross referenced
- Opportunistic at the general genetics clinic or after detection in any unfocused screening programme (CS)
- Sperm and ovum bank donor screening (CMFS)
- Arising from requests to exclude cystic fibrosis (CD)
- As part of research seeking subpopulations with increased carrier frequency—for example, pancreatitis or bronchitis clinic

Results are notified by a personal letter with offers of counselling when results are positive. The letter refers to risks of having affected offspring as low with no tests indicated in pregnancy for those in whom one partner is a carrier and the other negative (for example, risk one in 836, see figure 2) or extremely low when both are negative. Formal genetic counselling is arranged for all carrier couples detected.

On occasion cascades have started after detection of carriers without a family history. The box gives details of the sources of families offered carrier screening. Detailed cross referenced results held on computer are kept with a set of formal notes for each relative or couple. This will contain a copy of any referral letter and the genotypes, an extended family tree which shows the relation to the index case, and copies of letters to the tested subject or couple. A copy of these letters is sent to the general practitioner.

Results

A great increase in the number of relatives and partners tested followed introduction of active cascade testing. Table I shows uptake between September 1989, when the cystic fibrosis gene was discovered, and January 1994. There was a great increase from April 1993, when the active programme was introduced.

TABLE I—*Numbers of relatives or partners tested monthly, excluding parents of subjects known to have cystic fibrosis. Active cascade screening started in May 1993*

	Year					
Month	1989	1990	1991	1992	1993	1994
January		12	7	10	12	160
February		21	20	13	11	
March		12	11	13	19	
April		18	24	7	23	
May		18	18	6	44	
June		6	30	15	107	
July		14	21	0	87	
August		35	25	11	119	
September	11	17	27	15	133	
October	12	15	31	22	133	
November	15	8	13	12	178	
December	10	21	13	7	109	

Table II represents the present state of an ongoing process. It shows the number of families who are participating, the average number of relatives tested per family, and the number of index families and relatives who have decided not to participate or who have declined testing. More relatives on the mother's side have been tested than on the father's. The highest number of individual subjects from a particular family to have tests stands at 56. Table III gives the results in the relatives with the 12 mutations discovered in the total group. There are many family members of those with common and rare mutations still awaiting testing.

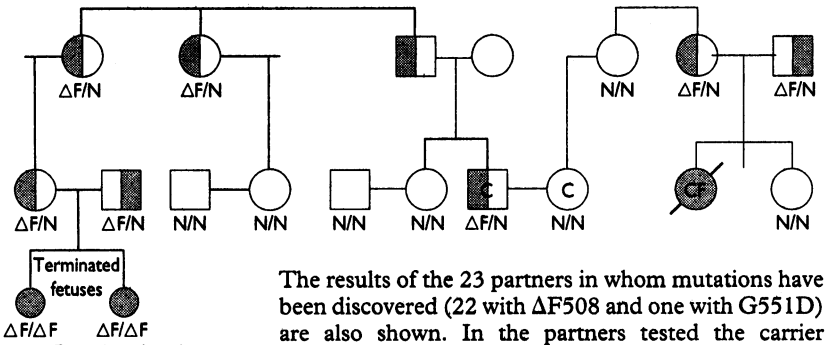

FIG 2—*Detection of carrier couple by cascade screening. C denotes original consulting couple. ΔF=ΔF508, N=negative result on Multiplex ARMS test*

The results of the 23 partners in whom mutations have been discovered (22 with ΔF508 and one with G551D) are also shown. In the partners tested the carrier frequency in this sample is one in 19, quite a lot higher than carrier frequencies found in the other screening programmes (see table IV.)

Table IV provides details of the 15 carrier couples detected, of the pregnancies and prenatal tests undertaken in this group, and of the outcomes of pregnancies. The couple who declined prenatal tests had a pregnancy 12 weeks under way when first tested. At the time of writing, this pregnancy was still ongoing and arrangements have been made to test the baby at birth.

Both couples who had amniocentesis presented after 12 weeks of pregnancy. DNA analysis by polymerase chain reaction on spun amniotic cells gave the same result when repeated on the cultured cells. In one of the couples, with the relative only partly informative on DNA testing and her carrier status not certain, microvillar enzyme tests were performed on the amniotic fluid. An affected fetus was predicted. The couple continued with the pregnancy, saying that the late diagnosis had influenced their decision. The diagnosis of cystic fibrosis was confirmed at birth. The second mutation (1898+1 (G >A)) has subsequently been found in this family.

On six occasions prenatal diagnosis was by chorionic villus biopsy at 9-10 weeks, including one couple who had two consecutive pregnancies. Results were reported in each case within 24 hours and often on the same day. The couple shown in figure 3 was detected on the distaff side of the family, with the relative negative and partner a carrier. A cascade in his family discovered a carrier couple with an early pregnancy under way. Chorionic biopsy revealed an affected fetus, and in a second pregnancy some months later an affected fetus was discovered again. On both occasions the couple opted for termination. This couple have been entered in a preimplantation diagnosis programme.

In several instances tests were done on couples who had completed their families but wished to know whether their children required testing. Two carrier couples were discovered in this way. Another carrier couple was reached through cascade though they had lost an affected child years before. Their carrier status was confirmed. They had been unaware of the details of the genetic discovery and arranged for their children to be tested. One diagnosis of cystic fibrosis was made directly through the cascade programme when a woman identified as a carrier through a research programme on pancreatitis proved to have a carrier husband. Their 4 month old son was found to be affected.

In table V the numbers of tests done in this and in other carrier detection programmes are compared. The cascade system is at least 10 times more effective at detecting carriers.

TABLE II—*Details of those accepting and declining tests* since start of active cascade screening*

Detail	Accepting tests and contacting relatives	Declining tests
Index families	129	12
Relatives on father's side	372	12
Relatives on mother's side	571	4
Average number (range) per family	16 (3-67)	

*Note: this is an ongoing process and individual people and families who decline have changed their minds. Not all known families have been contacted personally yet except by letter. Index families which decline imply that their relatives will not be informed of scheme through them.

TABLE III—*People tested in cascade screening programme 15 January 1994**

Detail	Relatives tested (n=1122)	Partners tested (n=441)
Tested negative	695	418†
Carriers	427	23
Mutations identified:		
ΔF508	364	22
G551D	28	1
621+1(G>T)	10	
R117H	5	
1898+1(G>A)	4	
1717-1(G>A)	3	
R553X	2	
W1282X	2	
G542X	2	
S549N	2	
R560T	2	
E60X	1	
1154insTC	1	
3659delC	1	
	427	

*Fifteen carrier couples detected (at one in four risk of having child with cystic fibrosis).
†Negative for ΔF508, G551D, G542X, and 621+1(G->T).

Discussion

All the successful carrier screening programmes, including this one, have included an active element. Bekker *et al* encapsulated this in an article

TABLE IV—*Details of carrier couples identified through cascade screening for cystic fibrosis*

Family No	Relation	Genotype*	Partner's genotype*	Pregnancy	Prediction*	Outcome/comments
1.034	Maternal uncle	ΔF508/N	ΔF508/N	Chorionic villus biopsy	ΔF508/N	Healthy newborn
2.257	Mother remarried	G551Δ/N	ΔF508/N	Chorionic villus biopsy	G551D/N	Healthy newborn
3.270	Sister	A/N† or N/N	ΔF508/N	Amniocentesis	Affected	Born affected
4.316	Mother remarried	ΔF508/N	ΔF508/N			
5.330	Maternal aunt	1717-1/N	ΔF508/N	Aminocentesis	ΔF508/N	Healthy newborn
6.374	Cascade† no family history	ΔF508/N	ΔF508/N	Chorionic villus biopsy Chorionic villus biopsy	ΔF/ΔF ΔF/ΔF	Termination Termination
7.391	Sister	ΔF508/N	ΔF508/N	Chorionic villus biopsy	N/N	Continuing
8.448	No family history	ΔF508/N	ΔF508/N			Affected infant†
9.516	Maternal uncle	ΔF508/N	ΔF508/N			
10.544	Paternal great uncle	ΔF508/N	ΔF508/N			Lost child with cystic fibrosis†
11.596	Cousin	ΔF508/N	ΔF508/N	Chorionic villus biopsy	ΔF/ΔF	Termination
12.632	Paternal aunt	3659delC/N	ΔF508/N	Declined prenatal test	1/4 chance of cystic fibrosis	Continuing
13.667	Cousin	ΔF508/N	ΔF508/N			
14.674	Paternal aunt	ΔF508/N	ΔF508/N			Family complete
15.920	Paternal aunt	ΔF508/N	ΔF508/N			About to have in vitro fertilisation

*N=normal allele, ΔF/ΔF=ΔF508 homozygote. Other abbreviation under genotypes refer to cystic fibrosis mutation. †See text for details.

TABLE V—*Comparison of carriers and carrier couples detected in this and other screening programmes*

Study	Number screened	Carriers detected	Carrier couples detected
Mennie *et al*[8]	3165	111	4
Watson *et al*[9]	1000	29	0
Bekker *et al*[7]	957	28	0
Wald *et al*[10]	338	13	0
Harris *et al*[11]	446	11	1
Present study (Cascade)	1563	450	15

which questioned whether high uptakes occurred more because of supply push than demand pull.[7] We admit that a strong element of our high uptake has been active promotion (though never coercion), dedicated staff, and a clearly laid out policy. Response from many family members has been positive, and we have received many supportive letters but none expressing negative feelings about the programme. We believe that relatives and those who marry into the family generally do want to know their carrier status but had sometimes not known how to go about it. We know of subjects who have wished to avoid hurting the feelings of an affected relative by asking for tests. Being made aware of the availability of testing by the index family removes this potentially negative dimension.

Cascade screening has generally been well accepted by the index families, who have been happy to contact relatives. There are those who show reluctance and no pressure is exerted. It is interesting to note that more tests have been done on relatives on the mother's side than on the father's, with more people declining tests on his side. We intend to explore this further. We have not specifically asked for reasons for why some relatives decline testing nor have we asked couples how they will use test information. Counselling has ensured informed decisions in those carrier couples detected. We hope that our explanatory letter and booklet help couples in which one or neither partner is found to be a carrier to understand their low risk of having affected offspring. We have had few requests for further information from this group, despite the fact that current negative testing is capable of reducing the carrier risk only by 88%.

Young people contemplating pregnancy tend to feel lucky, and we believe that negative results would tend to reinforce further these feelings—that is, they think that they are not carriers. Formal study of their reactions has not been undertaken. We have now a sizeable body of such people, and we hope to study short and long term reactions in the future. A few have been entered into a wider study of the impact of autosomal recessive disorders on families being conducted in collaboration with the centre for family research, Cambridge. Our fieldworker emphasises to family members that all of us carry a few genes for recessive disease and that the cystic fibrosis gene happens to be testable and the most common in Britain.

One specific study from Belgium has looked at the impact of being discovered to be a carrier of a cystic fibrosis gene (L Denayer *et al*, 18th European meeting on cystic fibrosis, Madrid, 1993). About 87% of the group had a family history of cystic fibrosis, and 12% were pregnant when tested. People found to be carriers had considerably fewer positive feelings about themselves compared with those who had tested negative. Immediate feelings included weakness, shock, anger, and stigma. Specifically there was no increase in guilt, shame, or of feeling ill. Interestingly, subjects all believed that others who might be detected as carriers would be more likely to express negative feelings than themselves. Thus coping mechanisms seem intact. We hope to study this more formally in future in our group.

Most of the families tested in our study have not had pregnancies under way. Nevertheless, pregnancy does concentrate the mind, and some relatives have come forward because of a pregnancy, and we receive several calls from staff at antenatal clinics who have been encouraged to include asking about a family history of genetic disease, including cystic fibrosis, in their clerking.

INCREASING THE OPTIONS

The ability to detect couples at risk before there are pregnancies increases the options of those planning a family. For a fully developed service we would like procedures such as preimplantation diagnosis to be available among the options.[20] Currently, couples who find themselves in this state have been prepared to have antenatal diagnosis with selective abortion and in this way they are similar to couples with affected children.[21] Discovery of couples at risk for a disorder when they themselves do not have an affected child, however, is rather different from the situation of parents of a child with cystic fibrosis. There would certainly be interest in this group for preimplantation testing if such a service were available. Nationwide one could expect interest from a considerable number of such couples, especially if one includes other common severe recessive disorders for which the same type of technology would be applicable. Such calculations should form part of planning decisions of preimplantation diagnosis services.

The detection of rare genotype carrier status in relatives adds an extra refinement to our cascade service. The existence of a national rare genotype testing service for cystic fibrosis, much like the National Haemoglobinopathy Service in Oxford, would allow the same sophistication to be achievable nationally. Our laboratory already has contracts with 11 health regions to search for rare genotypes in their known cases of cystic fibrosis, negative for the commoner mutations.

One difficult aspect of the cascade programme is the discovery of relatives who live outside our health region. General practitioners have sometimes ignored requests to organise local testing. We have accepted these by post at the families' request. Contact with the local general practitioner, genetic clinic, and sometimes obstetric service then follows.

Uptake of this service has proved even greater than expected. Often a particular family member becomes active in recruiting relatives for testing. Some have drawn up large and detailed family trees. It was originally thought that about 10 subjects (relatives and partners together) would come forward for testing for each of the 500 index families expected to take part. Our results to date and the continuing roll on effects of the cascade programme lead us to believe that an average of 20 people per family will be tested. The large size of families with cystic fibrosis is usually quoted in articles on heterozygote advantage.[22] Families in north west England are no exception. Our results allow us to predict that we will detect a carrier couple for every 100 relatives and partners together tested (currently about two thirds of those who come forward for tests are relatives of someone with cystic fibrosis). Thus we would expect that once the cohort of 10 000 have been tested we will have discovered around 100 carrier couples. In each pregnancy underaken by such a group there would be 25 affected fetuses, equal to the number of children born annually with cystic fibrosis in our region.

If similar schemes were introduced across Britain, where 6000 patients with cystic fibrosis are known,[23] 120 000 tests could result in discovery of 1200 couples at one in four risk of having affected offspring. Thus 300 affected pregnancies would theoretically be detect-

able, again equal to the number born with cystic fibrosis annually in the United Kingdom. Unfocused screening allows detection of about one carrier couple per 1000 tests performed (see table V); thus cascade testing based on a positive family history is 10 times more powerful, simply in arithmetical terms, not to mention the value of the foreknowledge of what cystic fibrosis implies in many of the carrier couples detected. If the true incidence of carriers in Britain is higher than one in 25, as our figures suggest, even more carrier couples would be detectable. One point which has been made is the limited effect which family based testing would have on carrier detection, with 90% of newly diagnosed cystic fibrosis occurring in the absence of a family history. Such estimates have been taken at face value. How many of us know our second and third cousins? We think that an active cascade programme may reach a greater proportion of the population at risk than some people expect.

The central starting point for cascade screening is the affected family. Modell has written recently on the important part which general practitioners may play in cystic fibrosis carrier screening, including promotion of cascade,[24] and we have seen this in action with increasing numbers of general practitioners arranging testing of relatives and participating in education and support after positive results. Certainly general practitioners could expand their role by choosing an individual doctor or practice nurse to concentrate on community genetic aspects of their practice, including cascade testing of relatives for cystic fibrosis and other recessive disorders which are amenable to this approach. Such practitioners would have established links through the fieldworkers of clinical genetics departments and would arrange for necessary testing and counselling. We have written to the general practitioners in our region through their district family practitioner offices recommending Modell's ideas to them and telling them of the regional cascade screening programme. It is also covered in detail at the annual departmental community genetics course, of which the latest was targeted at general practitioners.

EXTENDING CASCADE SYSTEM TO OTHER DISEASES

Cascade testing may start after any positive identification of a carrier and so forms a vital spin off of any screening programme, increasing immediately the chance of detecting carrier couples. If the present profession led impetus towards pregnancy testing does build up, early testing is better than late and cascade testing of relatives of detected carriers should form part of the programme. We are currently exploring the possibility of expanding our cascade system to include ß thalassaemia in our region. Many carriers are detected in the absence of a family history when undergoing simple blood count, with abnormal indices leading to further investigation. Response to offers of tests and counselling has been positive. Cascade would also be applicable to sickle cell disease and already operates in Tay-Sachs disease (S Simon, personal communication).

Cost-benefit analysis for avoidance of genetic disorders is crude and misses important human dimensions. That people show concern and wish to avail themselves of tests, with the advantages to most of their risks being found to be reduced after testing, is more important than financial considerations. At a purely financial level the cost of cascade programmes is economical when compared with unfocused screening measured by carrier couples detected; most such couples when faced with an affected pregnancy opt for termination saving the costs of care. In assessing the costs of an active cascade system, one presupposes the incorporation into regional genetic services with their existing infrastructure. Ideally, such savings could contribute to defraying the steeply rising costs of emerging new treatments.[25] The ultimate aim must be to have the most ideal treatment possible available to a smaller and smaller pool of affected people, with cascade screening seen as part of the global effort to conquer this and similar diseases.

Clinical implications

- Tests are able to detect 80-90% of carriers of the cystic fibrosis gene
- Generally uptake of the test has been poor
- Offering the test to relatives of known patients seems acceptable
- A high proportion of carrier couples could be detected and results could be used in family planning
- Most couples tested will be low risk and benefit from reassurance

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