Current topics

Screening for cystic fibrosis

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SUMMARY Practicable methods are now available for whole population screening of neonates for cystic fibrosis. Although diagnosis and treatment of the disease from birth has not yet been unequivocally shown to improve prognosis, existing evidence suggests that this is likely. Further ethical reasons are proposed in support of neonatal diagnosis and early treatment. The development of tests for prenatal diagnosis and carrier detection is under active investigation, and raises ethical problems for heterozygotes and their medical advisers. The heavy financial and emotional burden this disease imposes on the patient and the family should not be underestimated when policy decisions are made.

It is possible to screen all newborn infants for cystic fibrosis (CF), the most common serious inherited disorder in European children. Whether population screening for any disease should be undertaken on a national scale depends on criteria which were summarised by Wilson and Jungner¹ for the World Health Organisation in 1968. They proposed that screening is justified if (1) a disease is an important health problem for the individual and the community; (2) its natural history is known; (3) it has a latent or early symptomatic state; (4) it can be identified by a suitable screening test; (5) the facilities for definitive diagnosis and treatment are available and the treatment policy agreed; (6) the natural history of the disease is favourably modified by early, acceptable treatment; and (7) the exercise is cost-effective.

In an earlier review, Brimblecombe and Chamberlain² considered that these criteria were not met in the case of cystic fibrosis. In 1982, it would appear that only the last two remain to be satisfied although treatment policies differ between centres. This paper examines the present situation regarding neonatal, heterozygote, and antenatal screening for CF in the light of recent developments.

Methods for neonatal screening

Current neonatal screening tests are dependent on one of two clinical features of CF: a raised sodium chloride level in stimulated sweat, or the various

consequences on the composition of meconium, faeces, or blood related to developing pancreatic dysfunction in the fetus.

Sweat test. The normal Na⁺ or Cl⁻ concentrations in stimulated sweat from young children range between 10 and 50 mmol/l whereas in the sweat of CF patients the levels are between 75 and 150 mmol/l.³ The pilocarpine iontophoresis quantitative method developed by Gibson and Cooke⁴ is the procedure generally used and although simpler and more rapid procedures have been proposed none appears to approach the reproducibility and specificity of the Gibson-Cooke method.⁵ It does however have a number of drawbacks which make it impractical for routine screening. It is time-consuming, expensive, and requires trained personnel to carry it out if error is not to be introduced and, ideally, is best carried out on infants aged at least 1 month. Thus the sweat test is used if CF is already suspected.

Meconium test. Tests on meconium measure the indirect effect of pancreatic insufficiency. Most tests measure albumin which accumulates in the meconial mass from ingested amniotic fluid in the absence of pancreatic proteolysis. Albumin has a concentration of less than 0.1 mg/g in normal meconium and an average of 200 mg/g dry weight in CF meconium. It is either measured semiquantitatively by a test strip method⁶ or by various immunoassay methods.⁷⁻⁹ However, all such tests have a 0.5%

false-positive incidence which can be reduced to less than 0.1% by various additional tests such as the 'lactase test'¹⁰ or an estimation of albumin: α_1 trypsin inhibitor ratio.⁸ More importantly, up to 30% of CF meconium specimens give a false-negative result and there is currently no test on meconium which can reduce this false-negative incidence.

Faeces test. Unlike meconium tests, most faeces tests are based on the assay of tryptic or chymotryptic activity in specimens. The false-positive incidence is similar to that obtained with meconium screening but can be reduced to less than 0.2% by repeating the test on a second specimen.^{11 12} The false-negative incidence appears to be similar to that obtained with meconium screening. An advantage is that the test can be carried out on dried faecal specimens that have been smeared on a card. This simplifies collection, handling, and despatch to a central screening laboratory but there is the possible risk of infection for those handling the cards. A similar approach has been found to be applicable to albumin screening in meconium¹³ and is the basis of a nationwide screening programme in East Germany.

Blood test. Recently Crossley *et al.*¹⁴ reported that serum immunoreactive trypsin (IRT) content was 5 to 10 times higher in blood of newborn CF children compared with that in the blood from healthy neonates. The assay can be adapted to determine IRT content in dried blood spots similar to those collected for phenylketonuria and hypothyroidism screening. Retrospective studies carried out on blood spots up to age 5 years have not given consistent results concerning the specificity of the test¹⁵⁻¹⁷ but this could be owing to a number of factors including the nature of the filter paper and its storage. Prospective studies currently in progress confirm that it is considerably more specific than either the meconium or the faeces test and has a greatly reduced false-negative incidence.^{15 18 19} False-negative results may however occur in some but not in all children with meconium ileus.^{17 18} The major drawback of the test is that it is considerably more expensive than other CF screening methods. Also, commercial kit procedures for IRT estimation need to be adapted to detect IRT in blood spots. One company has revealed plans to market a kit designed for blood spot IRT analysis.

On current evidence the IRT test appears to be the most satisfactory screening method.

Advantages of early diagnosis

Clinical. Identification of presymptomatic infants with CF is justifiable only if irrevocable pathological

changes have not already occurred, and if it can be shown that progress of the disease is halted or appreciably retarded by treatment. Although the unknown basic biochemical defect expresses itself at birth by abnormal salinity of the sweat and by pancreatic damage, involvement of the lungs, which is the element of CF most likely to shorten life, does not begin until after birth. If lung damage were preventable therefore, diagnosis at birth followed by preventive treatment would offer the best prospect for long survival in good health. There are many who believe that early treatment with antibiotics, particularly antistaphylococcal agents, combined with physiotherapy, prevents or postpones serious lung damage. Some have spent a professional lifetime dealing with CF and can point to the steadily improving prognosis and increasing longevity of their patients since the advent of various antibiotics together with suitable measures for their delivery.^{20 21} Other equally respected physicians believe that intrinsic factors peculiar to individual patients are the most important determinants of prognosis, and that therapeutic variables play a fairly minor (but not necessarily unimportant) role.²² Unfortunately, no authoritative paper has yet been produced which gives data on the long-term results of treatment from birth in a large group of patients, compared with controls diagnosed by clinical presentation. Recent reports to an international cystic fibrosis conference indicated that in early childhood the clinical state of patients diagnosed by screening at birth was clearly better than that of children diagnosed later, but that the differences became less pronounced with age.^{23 24} Screening tests have now been used in pilot studies for more than 10 years, but unfortunately the variability in the clinical spectrum means that large numbers of patients must be followed and differences in management between centres make multi-centre studies and comparisons dubious: for instance, physiotherapy differs in techniques, frequency, and efficiency. Unequivocal data are therefore exceedingly hard to obtain.

This should not mean that introduction of neonatal screening must be indefinitely postponed. The benefits of early diagnosis of congenital hypothyroidism were apparent to clinicians long before neonatal screening was introduced, and the quality of life for numerous affected children, and their families, would have been greatly improved if a screening programme for hypothyroidism had been started when suitable techniques became available. There are times and circumstances when experienced clinical judgement should be given the benefit of the doubt and allowed to influence policy before final incontrovertible evidence can be obtained.

Beneficial effects of early treatment need not be

confined to the lungs. For example, attention to nutrition might be expected to improve growth, but it does not. Children who were diagnosed 'late'—that is after 6 months—were slightly but significantly taller and heavier for their age in later childhood than those diagnosed early (J G Yassa, 1981, unpublished data). The explanation for this paradoxical finding is probably that children presenting late have been fortunate enough to escape infection in the first few months when postnatal growth is particularly rapid, or perhaps they represent a milder genetic variant. Moreover, some impairment of growth seems to occur even before birth, the average weight of newborn CF babies being about 0.5 SD below the population mean.²⁵ Early optimal nutrition might however prevent other serious complications of CF—such as cirrhosis of the liver.

It is also possible that the time of diagnosis might affect parental compliance with treatment regimens, but we have no evidence that this is so.

Genetic. Most parents of CF children think very seriously before embarking on further pregnancies, once the genetic risks have been explained. Early diagnosis allows for genetic counselling and the adoption of contraceptive measures before the mother has had time to become pregnant again.

It is still not uncommon to diagnose CF for the first time in a child whose fairly minor symptoms have not been regarded as significant, but whose younger sibling has been identified by neonatal screening or early clinical presentation. Despite their lack of alerting features, such children may have finger clubbing, poor growth, cough, chronic diarrhoea, and extensive lung damage on radiological examination. Observation of the course of the disease in the younger siblings suggests that in many cases pathological changes of this severity are largely preventable.²⁰

Research. The value of individual preventive and therapeutic measures in CF can be assessed most effectively in patients who have not had the disease modified by previous treatment or by the development of secondary complications. Neonatal diagnosis identifies such a group of virgin cases. If screening were adopted on a large enough scale, it would allow valid comparisons to be made between the regimens employed in different treatment centres and facilitate controlled trials of treatment. In addition, population screening would help to identify hypothetical genetic variants of CF with good or bad prognosis.

Ideally, screening should therefore be linked with a programme of treatment and detailed, regular clinical, and radiological assessment. It should also

be linked with research programmes. This does not necessarily mean that affected children all need to be given their routine hospital care at a regional centre, but it does mean that they should all be notified to appropriate centres and their care and assessment carried out according to an agreed protocol.

Cost-effectiveness

The current cost of the IRT test is 40p per sample or about £640 per patient diagnosed. Technician costs are additional, up to a further 100% depending on the volume of work. Widespread adoption of the test would inevitably lower the cost. If early diagnosis prevents lung disease, it may save money by keeping patients out of hospital, although they would need to attend as outpatients. It is probable that intensive prophylaxis postpones rather than prevents lung involvement so that the ultimate cost to the services may be no different. It is therefore impossible to say whether or not screening represents a good economic investment. Given the fairly small price of screening, economic argument is probably irrelevant and the true cost should be measured in human and ethical terms. Few would claim that certain other medical activities undertaken for humanitarian reasons, such as terminal care, are cost-effective but none would doubt their value.

Ethical aspects

Can we justify screening if we cannot prove its actuarial benefits? We think so, for the following reasons:

- (1) If there is genuine doubt about its value which cannot be resolved, the basis should be in favour of early diagnosis and treatment. At least it will do no harm, and at best it may do much good.
- (2) Even if early treatment should not prove to affect the long-term prognosis in CF, screening and early intervention are a demonstration of concern by the 'caring' professions. Avoidable delay in diagnosis produces resentment which is directed towards the general practitioner or the hospital services.²⁶ Maintenance of a good doctor-patient and doctor-parent relationship is essential for optimal control of the disease.
- (3) The parents will be spared the feelings of guilt that come from having overlooked early symptoms themselves, and also those occasioned by unwittingly bringing additional affected children into the world.
- (4) A screening programme would not be disproportionately resource-consuming; it would not greatly affect or take away from other major activities within the health services.

Against these arguments must be weighed the emotional effect on the parents of normal babies of the occasional false-positive test.²¹ For some of these parents there will be genuine distress until the diagnosis of CF can be eliminated, but for most the blood test can be repeated without necessarily raising anxiety. In the very few cases where a sweat test is required, the parents' worry should be quickly overcome by their relief. There is also the possibility that false-negative results may induce a false sense of security so that the disease is not suspected when the child subsequently develops symptoms of CF. The limitations of the screening method must therefore be clearly understood.

Can we therefore justify not screening? Only if it can be proved that current treatment is not effective or that delay makes no difference. Modern management, although far short of offering cure, demonstrably improves longevity and the quality of life, especially when started early.²⁰ When the basic defect is identified and treatment directed at the primary abnormality is introduced, screening will become mandatory, but a cohort of patients will have been deprived of its full value. The case for neonatal screening must be put to health service administrators, but a decision not to screen must be justified to those CF patients who are undiagnosed or yet unborn, and to their parents.

Heterozygote screening

Until now, the only method of diagnosing the CF carrier was by inference: parents of affected children are obligate heterozygotes.

There are perhaps three main areas where a reliable heterozygote screening test would be of great use. Firstly, the identification of 'at risk' pregnancies by screening all women at their first pregnancy, and in those found to be heterozygotes, screening their partners. If the partner is also a carrier there will be a 1 in 4 risk that the fetus has the disease. Assuming a reliable prenatal test (see later) such women can then be screened for an affected fetus. Secondly, unaffected siblings and more distant relatives of a CF child often wish to know whether they and their partners are also heterozygotes. Thirdly, it would be very useful to identify CF carriers who have not been in contact with a CF child. Living in constant proximity to a child or children with repeated chest infections etc may well cause immunological changes that are independent of carrier status, but which may masquerade as manifestations of the gene defect. It is possible that certain 'CF proteins' could be of this nature.

Currently there would appear to be at least 4 possible tests that are under investigation:

Immunoassay detection of a related protein. Recently Manson and Brock²⁷ reported the production of an antibody against a serum protein they considered to be similar to the 'CF factor'. Using the fairly simple electroimmunoassay method they were able to distinguish between the serum of CF patients, obligate heterozygotes, and normal subjects.

Currently, a double-blind study is in progress to determine the specificity of the assay (D J H Brock, 1981, personal communication). Brock considers that the protein being measured is unlikely to be the same protein as the factor causing ciliary dyskinesia in rabbit tracheal organ culture which was described by Spock *et al.* in 1967.²⁸

Abnormal Na ion transport in fibroblasts. Breslow *et al.*²⁹ recently reported that CF and CF heterozygote fibroblasts accumulated less than half of Na²² compared with normal fibroblasts when incubated with Na²² in the presence of ouabain. The difference was striking and clear. However they were unable to distinguish between normal subjects and heterozygotes in a follow-up blind study.³⁰ The need to culture cells would also eliminate this method from use in routine screening.

The CF 'lectin'. A factor in CF and heterozygote serum which agglutinates mouse red blood cells has been described. The agglutination occurred only in the presence of serum IgM and was inhibited by fructose and a wide spectrum of other monosaccharides.³¹ Despite initial encouraging results, a blind study indicates low specificity of the test and at least one other laboratory has been unable to reproduce Lieberman's original findings.³²

Heat inactivation of plasma hydrolases. It has also been reported that serum α -mannosidase and acid phosphatase were more thermo-labile in CF serum than in normal controls. By using certain stringent conditions, there was little or no inactivation of the hydrolases in normal serum, 50% inactivation in heterozygote serum, and total inactivation in CF serum.³³ Unfortunately the work has not been reproduced outside the original laboratory although visitors working there can succeed but cannot do so once they have returned to their own laboratories (H Kollberg, 1981, personal communication). The one blind study so far reported was done on only 12 specimens, far too few on which to make an assessment.³⁴

Prenatal screening

Two possible methods are currently being evaluated:

MUGB arginine esterase. Nadler's group working in Chicago claimed to have developed a reliable screening test that can be carried out on amniotic

fluid.³⁵ Using an active site titrant, methylumbelliferylguanidinobenzoate (MUGB) for assay purposes, a benzamidine-inhibited arginine esterase was found to be significantly reduced in the amniotic fluid of a CF fetus.

Apart from reduced active site-titrant binding, the esterase in CF is characterised by the absence of a 200 000 MW component present in normal amniotic fluid. It also separates into three rather than the normal four bands in a polyacrylamide isoelectric-focusing system. It was suggested that all three criteria should be investigated before making a final diagnosis.³⁵ In the first 49 pregnancies monitored, there were 3 false-negative and 1 false-positive result³⁶ while an attempt to reproduce the methods in another laboratory, using stored amniotic fluid, would have resulted in misdiagnosis of all 3 cases of cystic fibrosis tested using the MUGB reactivity values, and at least 2 would also have been false-negatives with the isoelectric focusing test.³⁷ Early enthusiasm for the test has rapidly waned.

Abnormal hydrolase metabolism in cell culture. Hösli and Vogt have developed a number of methods based on their original finding of a defect in hydrolase metabolism after exposing cells to an 'indigestible' macromolecule.³⁹ As with the heat inactivation test (which is also one of the prenatal tests) their work has not been reproduced outside their own laboratory. Recently the results of this screening programme on 34 at-risk pregnancies were reported. Seven were positive of which only 3 were allowed to come to term and were found to have CF. There were also 2 possible false-negative results.³⁸

If either test should prove to be reliable, many known heterozygotes would embark on pregnancy. We have already referred to the expressed wish of parents for a reliable test that would allow them to have further children without the risk of CF. This implies acceptance of abortion if the fetus is found to be affected, and is of course a personal decision. Despite the great improvement in outlook for CF patients during the last few decades, no one should doubt the enormous physical and emotional burden which the disease imposes on them and their families.²⁶ Termination of pregnancy should not be withheld on the grounds of the improving prognosis for CF without understanding the cost at which this improvement is achieved.

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Received 16 February 1982

Commentary

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There has been a pronounced improvement in the outlook for children with CF during the last 20 years and major clinics in North America and Australia now report an 80% survival to late adolescence and

early adult life whereas 30 years ago fewer than 10% were alive at age 5 years. However, CF remains an important cause of morbidity and premature death, being responsible for 1 in 40 deaths between 1 and 14 years of age in England and Wales.

It was hoped that early diagnosis and prompt institution of treatment would retard or even prevent progressive lung disease. On this basis there has been considerable interest during the last 10 years in the development of newborn screening. Measurement of immunoreactive trypsin in a dried blood spot seems to have acceptable sensitivity and specificity as a screening procedure.¹ Dodge and Ryley make a strong plea for its widespread use.

However, before such a programme is introduced it is important to assess critically evidence in its favour, particularly the possible benefit of early diagnosis. Data in the literature are inconclusive.² We have been interested in this problem in Victoria, Australia, where there is a long-term epidemiological study of CF.^{3,4} Data are available on 580 patients born in Victoria between 1955 and 1978 and diagnosed by the end of 1979. The median age at diagnosis in the group was between 7 and 9 months and 68% of them were diagnosed before 12 months. It is believed that nearly all diagnosed patients are included and because of the nature of paediatric services in Victoria the number of patients dying undiagnosed is probably small. Such an unselected population provides considerable advantages for study over groups from clinics which see only referred patients.

In Victoria the survival of 39 patients diagnosed by 6 months because of family history and before the development of lung disease was not appreciably better than that of their 36 symptomatically diagnosed older siblings, nor was it better than that of other CF patients. Currently 95% of children and teenagers in Victoria with CF are managed in one clinic. Lung disease in 28 presymptomatically diagnosed children was not significantly less extensive than in other CF children. Sixteen presymptomatically diagnosed patients with living older CF siblings did not have significantly less extensive lung disease than those siblings.

The failure to demonstrate benefit from early diagnosis probably reflects the great variability of CF and the palliative nature of present treatment.

Dodge and Ryley suggest that newborn screening may prevent parents undertaking a further pregnancy if they already have an undiagnosed child with CF. In Victoria between 1967 and 1979 24 such children from 22 families were diagnosed as a result of finding the disease in a sibling. During the same period a total of 328 children presenting with symptoms or found by case detection was diagnosed so that at