KING'S FUND FORUM

CONSENSUS AND CONTROVERSY IN MEDICINE

Screening for fetal and genetic abnormality

Programme and Abstracts

The fourth in a series of consensus development conferences

November 30, December 1 and 2, 1987
REGENTS COLLEGE INNER CIRCLE
REGENTS PARK, LONDON NW1

£5.00

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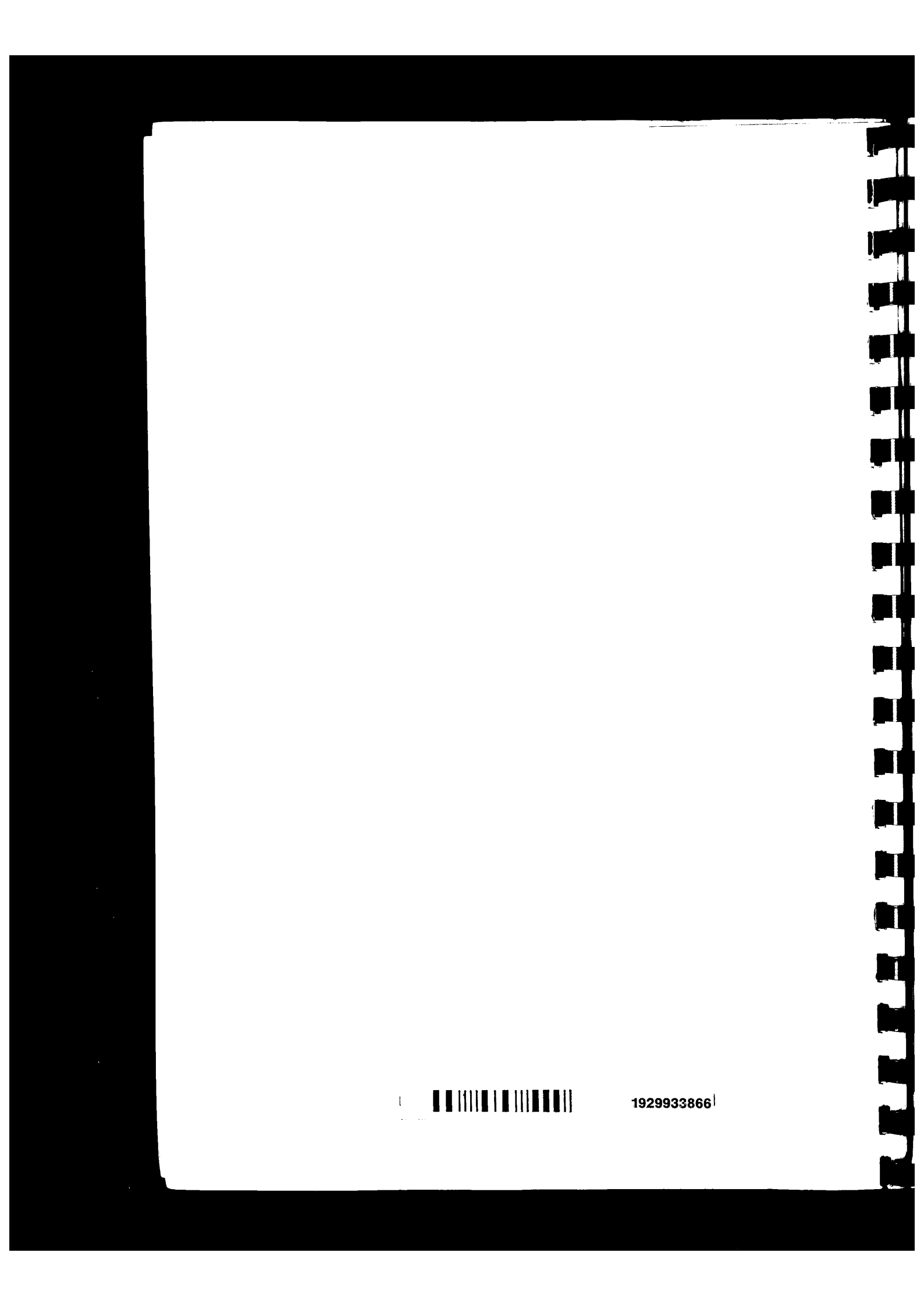
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INTRODUCTION

With the decline of infectious diseases as the major cause of perinatal mortality and handicap, congenital malformations and genetic disorders now account for up to 40 per cent of childhood deaths and three quarters of serious handicap. Screening to identify families at risk and antenatal detection of fetal abnormality has now become technically possible for an increasing range of disorders.

During this conference the evidence about these screening tests and investigations will be assessed and a consensus statement produced by the panel. The statement will give the panel's conclusions on screening for genetic and fetal abnormality to help professionals, the public and managers make decisions about individual and societal risks, benefits and priorities. The conference will consider the availability of screening programmes for those who wish to make use of them.

Consensus development conferences as initiated in the United States of America at the National Institutes of Health, take a specific medical technology or procedure and assess its application in health care. A unique feature of the process is that a panel, from a broad range of backgrounds, listens to the evidence presented by experts and views from the audience and prepares answers to a set of questions about the technology or procedure. The conference is open to the public to participate with the professionals in this process.

The expert evidence will be presented to the forum panel and the audience for the first day and a half. The panel will then retire to prepare answers to the pre-posed questions. This statement will be discussed by the audience on the Wednesday afternoon and changes may be made, at the panel's discretion before a press conference later that afternoon. The five questions which the panel will be asked to address are:

1 What kinds of screening and diagnostic tests are possible for genetic and congenital disorders?

2. What are the benefits and costs of these tests?

3. What social and ethical issues arise?

4. What criteria should be considered when determining the provision of these screening programmes?

5. How should these screening programmes be organised, and their performance monitored?

GENERAL INFORMATION

Conference sessions will take place in the Tuke's Hall, Regents College.

Telephone:

During the conference, messages can be left for those attending on 01-486 0141.

Catering arrangements (in Herringham Hall):

30 November - Coffee, lunch and tea

1 December - Coffee and lunch

2 December - Tea

Microphones:

Speakers from the floor are asked to use the aisle microphones and to identify themselves by name and affiliation.

Consensus statement:

The final statement will be sent to all participants after the conference.

AGENDA

November 30, 1987

09.00	Registration	
09.15	Welcome and introduction to the Conference	Ms B Stocking, Director King's Fund Centre Professor Grimley Evans

SECTION 1: INTRODUCTION

09.30	Reproductive choice and outcome	Dr M Richards, Lecturer in Social Psychology University of Cambridge
09.50	Genetic and congenital disorders	Dr M Pembrey, Professor of Paediatric Genetics, Institute of Child Health
10.10	Discussion	
10.30	Coffee	
10.50	The epidemiological principles of screening	Professor N Wald, Head of the Department of Environmental and Preventive Medicine, St Bartholomew's Hospital
11.10	Discussion	
11.20	Obstetric techniques	Professor C Rodeck, Professor of Obstetrics and Gynaecology Queen Charlotte's Maternity Hospital
11.40	Discussion	

SECTION 2: SCREENING FOR CONGENITAL MALFORMATIONS AND CHROMOSOMAL ABNORMALITIES

12.00	Screening for neural tube defects and Downs syndrome	Professor M Ferguson-Smith, Professor of Pathology, University of Cambridge

12.20	An obstetric view of population screening programmes	Professor B Hibbard, Professor of Obstetrics and Gynaecology, University Hospital of Wales
12.35	Discussion	
13.15	Lunch	
14.15	Screening policies: the present situation and beyond	Dr H Cuckle, CRC Senior Lecturer, Department of Environmental and Preventive Medicine, St Bartholomew's Hospital
14.30	Discussion	
14.45	Women's experiences and attitudes to screening	Dr S Macintyre, Director, MRC Medical Sociology Unit, University of Glasgow
15.05	Discussion	
15.30	Economic evalation	Mr J Henderson, Associate Research Fellow, Health Economics Research Unit, University of Aberdeen
15.50	Discussion	
16.15	Tea	

SECTION 3: SCREENING FOR INHERITED DISEASES

16.35	Cystic fibrosis	Professor D Brock, Professor of Human Genetics, University of Edinburgh
16.50	Impact on the family	Mrs C Lavery, Honorary Secretary, The Society for Mucopolysaccharide Diseases
17.05	Discussion	
17.45	Adjourn	

<u>December 1, 1987</u>

09.00	The haemoglobinopathies	Dr B Modell, Consultant in Perinatal Medicine, University College Hospital
09.20	Counselling	Ms E Anionwu, Head of Brent Sickle Cell and Haemoglobinopathy Centre, London

09.35	The patient view	Ms M McTair, Director, National Sickle Cell Programme
09.50	Discussion	
10.15	Huntington's chorea	Dr A Harding, Senior Lecturer in Neurology, The National Hospital for Nervous Diseases
10.30	Genetic risk	Mr S Thomas, Medical Writer,
10.45	Discussion	
11.00	Coffee	
11.20	Open Session	Audience presentations
11.40	Moral and ethical issues	Professor G Dunstan, Honorary Research Fellow, University of Exeter
11.55	Discussion	
12.15	Organising screening programmes for the new genetic techniques	Professor R Harris, University Professor, Dept. of Medical Genetics, University of Manchester
12.30	The future	Professor Sir David Weatherall, Nuffield Professor of Clinical Medicine, University of Oxford
12.50	Discussion	
13.00	Lunch and adjourn	

December 2, 1987

13.00	Presentation of consensus statement	
14.45	Close of conference	
	Tea	
16.00	The formal statement will be available.	
16.15	Press conference	

CONSENSUS PANEL

Professor Alberman trained at Cambridge and the London Hospital Medical School. After doing pathology for two years she spent a year at the London School of Hygiene and took the Diploma of Public Health. The training she received enabled her to take up a post as epidemiologist working on the causes of cerebral palsy at the Paediatric Research Unit, Guy's Hospital, London. She was then seconded to work on the 1958 National Child Development Study, before returning to Guy's to study the causes of spontaneous abortions. She then returned to the School of Hygiene to research into babies of low birthweight. She was appointed to her present position as Head of the Department of Clinical Epidemiology at the London Hospital in 1979 and has retained an interest in reproductive epidemiology.

Miss Ashton SRN SCM, joined the Royal College of Midwives as Senior Tutor in 1975 and was appointed Professional Officer in 1979. Later that year she became Acting General Secretary and in 1980 (to the present time) General Secretary. She was the first Chairman of the EEC Advisory Committee on Training for Midwives and is the Hon Secretary of the Joint Committee for Professional Nursing, Midwifery and Health Visiting Associations in England; Secretary/Treasurer of the EEC Midwives Liaison Committee; Member of the Council of Birthright; Hon Secretary of the Iolanthe Trust; Member of the Steering Group working on the DHSS Strategy for Nursing Projects; and occupies a seat on the Nurses and Midwives Staff Negotiating Council.

Professor Bobrow was born in South Africa, and qualified in Medicine in Johannesburg. He came to the UK after a few years in general clinical medicine and was appointed to the MRC Population Genetics Unit in Oxford and subsequently to the Regius Department of Medicine and Oxford University Genetics Laboratory. He was appointed Consultant in Medical Genetics in Oxford 1981 and Prince Philip Professor of Paediatric Research, UMDS at Guy's Hospital and Director of South East Thames Regional Genetics Centre in 1982. His special interests have been in gene mapping, the muscular dystrophies and prenatal diagnosis.

Peter Coe was educated at a Hampshire Grammar School and read Medieval History at York University. He spent a period of time working as a conservation officer for the Church of England and entered the NHS in 1971 as a National Administrative Trainee. He has worked in East Anglia, Trent and Mersey Regions, in mental illness, district general hospitals and in the community. In 1979 he went to Barking District as Deputy District Administrator and in 1982 took up his present post as Director of Planning and Information for North West Thames Regional Health Authority.

Professor Culyer was educated at King's School Worchester and Exeter University. He has worked in University Departments in Los Angeles, Exeter and for the Ontario Economic Council. He became Professort of Economics at the University of York in 1979. His particular interests are, health indicators and public finance and social policy.

Professor Grimley Evans, read Natural Sciences at Cambridge and Clinical Medicine at Oxford with postgraduate training in Epidemiology in Oxford, the University of Michigan and in New Zealand. His early research work included the study of the effects of lifestyl e on health of migrant Polynesians of the South West Pacific. His present reserch interests centre on the prevention of chronic disability. He was Professor of Medicine (Geriatrics) University of Newcastle upon Tyne 1973-1984 before his present appointment as Professor of Geriatric Medicine, University of Oxford, Consultant Physician with a special responsibility for the elderly, Oxford Health Authority.

Dr Hall is married with two children. She graduated MB ChB and MD from Aberdeen University and is now a Fellow of the Royal College of Gynaecologists. She is Consultant Obstetrician and Gynaecologist in the Aberdeen Teaching Hospitals and Honorary Clinical Senior Lecturer in the University of Aberdeen. Her research interests are in antenatal care, pregnancy epidemiology (especially intergenerational and pregnancy career studies).

Dr Higgs initially read classics at Christ Church College, Cambridge but changed to read medicine. He spent his student clinical years at the Westminster Hospital and was a registrar in fevers before going into general practice in 1974. He took over his present practice in the Walworth Road, Camberwell in 1975. He became Senior Lecturer and Head of the academic department of general practice at King's College Hospital Medical School in 1981. He is a founder member of the Journal of Medical Ethics and one of the Directors of the Centre for Law and Medical Ethics at King's College. His special interests are the health problems of inner city dwellers, adolescent psychosexual issues and long term illness.

Marianne Rigge graduated from University College, London in 1970. She joined the Consumers' Association shortly after and has worked in the consumer movement ever since. In 1983 she became founder director of the College of Health and has been editor of its journal, Self-Health since 1985. The College of Health which now has more than 10,000 members has campaigned on behalf of the consumer on a range of issues including the nutritional quality of hospital food, patient access to medical records, the need for better patient information about drugs and hospital waiting lists.

Professor Rose Professor of Applied Social Sciences, University of Bradford

Professor Alwyn Smith qualified in medicine in Birmingham in 1952, then worked with Professor Thomas McKeown for three years and presented a PhD thesis on the epidemiology of congenital malformations. Following a DPH at the London School of Hygiene, he worked in Singapore, Dundee, Edinburgh and Glasgow before appointment to the Chair of Community Medicine in Manchester in 1967. He moved to his present Chair of epidemiology and Social Oncology in 1979. He has particular interests in population screening.

Professor Weale was educated at Varndean Grammar School for Boys in Brighton and at Clare College Cambridge where he read Theology. When he graduated in 1971 he went on to write a thesis in the field of Social Philosophy on the subject of equality. In 1974 he became Research Fellow in the Department of Politics, University of Newcastle and in 1976 became Lecturer in Politics, University of York. He stayed there for nine years developing a special interest in the ethics of health policy. In 1985 he moved to the University of East Anglia where he became Professor of Politics. As well as his teaching responsibilities for undergraduate students, especially in the field of social and political theory and the politics of the welfare state, he has research interests in the ethics of health care policy and in the administrative structure of environmental regulations.

SPEAKERS

Ms Anionwu is an SRN and HV Tutor. She is presently registered for a PhD at University of London Institute of Education (Subject: Identification and Development of Health Education and Counselling Provisions for Sickle Cell Disorders in Brent). Her present post is head of the Brent Sickle Cell and Thalassaemia Centre, Willesden Hospital, London. The Centre has developed information, screening and counselling services for Haemoglobinopathies.

Professor Brock trained as an organic chemist in Cape Town and Oxford Universities, and then moved to biochemistry and biochemical genetics during post-doctoral fellowships at Massachusetts Institute of Technology and Harvard University. Since his appointment to the University of Edinburgh, he has developed a wide-ranging interest in human biochemical genetics and especially in the prenatal diagnosis of congenital malformations. He was elected Fellow of the Royal Society of Edinburgh in 1983 and awarded the first Margaret MacLellan Award in 1986.

Dr Cuckle was educated at the Universities of Leeds and Oxford. Since 1975 he has worked in the field of epidemiology and preventive medicine in Oxford, Tel Aviv and London. His main research interests centre around screening for cancer in adults, antenatal screening for congenital abnormalities as well as elucidating the principles of screening. In the field of antenatal screening, his main contributions have been in the development of the scientific basis for alpha-fetoprotein screening for neural tube defects and Downs syndrome, and the subsequent diagnostic amniotic fluid tests.

Professor Dunstan is a priest of the Church of England. He is Professor Emeritus of Moral and Social Theology in the University of London; Honorary Research Fellow at the University of Exeter, Honorary Member oof the Royal College of Physicians and Honorary Fellow of the Royal Society of Medicine.

Dr Harding graduated in medicine at the Royal Free Hospital School of Medicine, London, in 1975. She trained in neurology at the Royal Free and Middlesex Hospitals, the National Hospital for Nervous Diseases and Hammersmith Hospital, London gaining experience in clinical genetics by working in the MRC Clinical Genetics Unit, Institute of Child Health. Her current clinical and research interests include degenerative ataxias, inherited neuropathies, spinal muscular atrophies and movement disorders. She is now Reader in Clinical Neurology at the Institute of Neurology. She co-runs a genetic counselling clinic at the National Hospital for patients with inherited disorders of the nervous system and their families.

Professor Harris qualified in medicine in Liverpool and trained originally as a general physician. He first became interested in genetics while doing an intercallated BSc, but it was a chance meeting with Professor Herbert Giles in 1960 during a field trip to Nigeria that began his study of human genetic resistance to disease. He became director of the Department of Medical Genetics in Manchester and set up a tissue-typing service to support the kidney transplant programme. He is a past president of the Clinical Genetics Society and is active in national planning of genetic serrvices and in encouraging undergraduate and postgraduate genetic training in genetics.

Mr Henderson read economics at York University and is an Associate Research Fellow at the University of Aberdeen. His main research areas are the economics of preventing ill health, the demand for primary health care and the evaluation of options for health service developments.

Professor Hibbard qualified in medicine from St Bartholomew's Hospital. He was appointed FRCOG in 1965. His main interests are in perinatal mortality, the diagnosis and prevention of fetal malformations, antenatal education and medical education.

Mrs Lavery formed the Society for Mucopolysaccharide Diseases in 1982 following the death of her first child Simon, then aged 7 years, who suffered from Hunter Disease - Simon was diagnosed at 21 months. Besides running the MPS Society, now an international voluntary organisation, she is funded by the Mental Health Foundation to provide training, management and organisation experience for other rare-handicap voluntary support groups. She works closely with other agencies including Contact a Family and the In Touch Trust.

Dr Macintyre is a medical sociologist. Her PhD was on 'Decision-making following pre-marital conception'. She has since conducted a number of other studies in the field of human reproduction, in the course of which she has followed couples through pregnancies, observered interactions in antenatal clinics and labour wards and interviewed obstetricians and midwives.

Ms McTair has been involved in working with people with Sickle Cell Disease for the past nine years, first as a Research Fellow and Graduate at Howard University, Washington D.C. USA then as a research fellow with King's College Hospital Medical School. She founded the Lambeth Sickle Cell Information Centre. For the past two years she has been the Director of the National Sickle Cell Programme, which is a Voluntary Organisation whose main aim is the education and training of professionals and the community at large on Sickle Cell disease. She is a trained nurse and worked as a community midwife and health visitor for 14 years before going to the USA.

Dr Modell is married with two children. She took a degree in Zoology at Oxford (1955) and a PhD in Developmental Biology at Cambridge (1959) before studying medicine at Cambridge and University College Hospital, London. Since registration she has concentrated on clinical research in the management and prevention of thalassaemia. Her involvement in prenatal diagnosis has led to a part-time NHS appointment to provide a service for thalassaemia in the North East Thames Region.

Dr Pembrey, Professor of Paediatric Genetics, Institute of Child Health

Dr Richards, Lecturer in Social Psychology, University of Cambridge

Professor Rodeck qualified at University College Hospital, London in 1969. Having specialised in high-risk obstetrics, he developed an interest in fetal medicine and surgery which he pursued as Director of the Harris Birthright Research Centre for Fetal Medicine at King's College Hospital, London. He was appointed Professor of Obstetrics and Gynaecology at the RPMS Institute of Obstetrics and Gynaecology, Queen Charlotte's Maternity Hospital, London in 1986. He is now a leading authority in fetal medicine and surgery with a particular interest in prenatal diagnosis and

Professor Ferguson Smith graduated in medicine from Glasgow University. He pursued his career in pathology and genetics mainly in Glasgow and at the John Hopkins Hospital USA. He became Professor of Medical Genetics, University of Glasgow from 1973, before moving to Cambridge this year.

Mr Thomas read history at Oxford and law in London. As a one-time consumer of genetic counselling, he has a keen interest in the evolution of medical genetics. His papers on the subject have been read to the British Psychological Society and published in the British Medical Journal. His book **Genetic risk**, subtitled **A Book for parents and potential parents** was published by Penguin in 1986.

Professor Wald Head of Department of Environmental Medicine, St Bartholomew's Hospital

Professor Sir David Weatherall qualified in medicine from Liverpool University. After serving in the R.A.M.C in Singapore and Malaya, he went to the John Hopkins Hospital, USA, as a research fellow in genetics. He pursued a career in haematology and medicine becoming Professor of Haematology in Liveerpool in 1971 and Nuffield Professor of Clinical Medicine at Oxford University in 1974. He is a fellow of the Royal Society.

PLANNING COMMITTEE

For this conference the Planning Committee consisted of: Ms B Beech, Professor A G M Campbell, Dr H Cuckle, Professor M Ferguson-Smith, Professor B Jennett, Dr I A F Lister Cheese, Dr B Modell, Dr Ann Oakley, Dr M Pembrey, Professor C Rodeck, Dr J Spiby, Ms B Stocking.

ABSTRACTS

The following are abstracts of the presentations to be given at the forum. They are designed for the use of the panel and audience and as a reference document for those interested in the conference deliberations.

We are grateful to the authors who have summarized their material and made it available in timely fashion.

SOME REFLECTIONS ON FETAL DIAGNOSIS

Dr M Richards
Lecturer in Social Psychology
University of Cambridge

In the last decade or so one of the fastest growing areas in medicine has been the development of techniques for fetal diagnosis for an ever growing list of genetic diseases and congenital malformations.

The main technologies that are involved are ultrasound screening, amniocentesis, fetoscopy, chronic villus sampling (CVS) and a wide range of biochemical, tissue culture and gene probe methods for the examination of fetal samples (see Wald 1984).

Surprisingly, the use of these methods have attracted relatively little public discussion and, with a few exceptions, social scientists have done little work which would help us to understand how parents and their families feel about these developments and the social and psychological impact they may be having.

It is my role in these opening remarks to sketch out some of the problems that we may wish to keep in mind during the discussions of the next few days.

Of the social science research done, much of this is preliminary and usually involves small and often selective samples (for general accounts see Farrant, 1985; Katz Rothman, 1987; Beeson, et al, 1983). We must also remember that the picture is not static. As new techniques are developed and employed, new issues and questions arise. Public knowledge and attitudes may change.

I aim to point to some of the social and ethical questions that I feel are important. I am not going to deal with technical and medical problems in the area - issues such as the comparative safety of amniocentesis and CVS or the false positive and negative rates of various diagnostic procedures - nor will I discuss the legal ramifications of the new technologies. These will be the topic of other presentations.

A distinction should be drawn between the situation for someone who receives news of a serious fetal condition as a result of a screening programme and those who know themselves to be at particular risk before the investigative procedures begin.

Knowledge of risk may result from awareness of carrier status of a genetic disease, because of a family history, or because an affected child has already been born.

It would seem that it is not simply the element of surprise for the screened mother - the bolt from the blue - but it is also because she may feel differently about her fetus than another mother who knows before conception that there is a significant risk of abnormality. The mother at risk is much more likely to have knowledge about the condition (e.g. Mouzouras et al, 1980) and is not faced with the same difficulties in assimilating a great deal of information very quickly when she is probably already disturbed and upset by the news of the unexpected and unwelcome diagnosis. I suggest that support from friends and relatives is more likely to be effective and forthcoming for the mother who knows her baby to be at risk. This may be especially important when a family knows something of a gene it carries or the parents belong to a community that is aware of its particular problem - such as the Cypriot community and beta thallasaemia (Modell et al, 1984).

Another difference between the high risk and screened groups concerns the balance of benefits and hazards in the two situations. Where the risk of an affected fetus is low, the chances of damage arising from the diagnostic techniques becomes relatively more important.

So, for instance, there will be a point where the chances of losing a normal fetus by miscarriage after amniocentesis will outweigh the advantages of finding a fetus with a serious disorder.

Risk groups may demonstrate one of the most obvious benefits of prenatal diagnosis in terms of reproductive patterns. With beta thalassaemia, for instance, there is evidence that before prenatal diagnosis was available, parents often curtailed further births after having an affected child and understanding their genetic situation. With prenatal diagnosis and abortion parents often go on to complete their originally planned family size (Cowan and Kerr, 1986).

The reassurance available through prenatal diagnosis may encourage women over 35 to have children (Roghmann and Doherty, 1983).

Few publications say much about the provision of information aimed at pregnant women and their partners or in classes for young people on parenthood. Where there is mention of fetal diagnosis in the media the position taken is often misleading, concentrating on the technologies and giving an over optimistic impression of the benefits and paying little attention to the hazards and complications or the emotional and ethical dilemmas that may be posed (see below).

(a) Abortion

With very few exceptions, fetal diagnosis of genetic disease and malformation cannot lead to any treatment of the fetus or change in the medical care of the mother. It has only three prime purposes: to permit the abortion of the fetus, to prepare a mother and her family for the birth of an abnormal child or, for those for whom no positive diagnosis is made, to rule out any of the disorders for which diagnosis is possible. One other rather special case I will return to later, is the determination of the sex of the fetus.

'Medical' abortions are a very small percentage of the total. In England and Wales in 1985 141,101 legal abortions to resident women were notified (OPCS, 1987). Of these, 1,921 involved the ground that 'there is a substantial risk that if the child were born it would suffer from such physical or mental abnormalities as to be seriously handicapped' (The Abortion Act, 1967); 1.4 in percentage terms. As one would expect, this proportion becomes much more significant with those abortions carried out later in pregnancy. 15.5% of the 2,116 abortions carried out after 20 weeks were for these 'medical' reasons.

These abortions are particularly distressing to women and may have longer term sequelae (Blumberg et al, 1975; Donnai et al, 1981; Leschot et al, 1982). This is because they are often 'late' abortions as well as of wanted pregnancies. The crisis reaction is comparable to that experienced after a perinatal death (Jorgensen et al, 1985; Lloyd and Laurence, 1985). Counselling and support may be inadequate (Farrant, 1980).

At present, as has been the case for a generation or more, abortion law is under discussion. A small minority condem all abortion and so oppose fetal diagnosis. Wendy Farrant (1985) has pointed to a significant group of clinicians and politicians who oppose abortion on social and psychological grounds but support and even promote it in the context of fetal diagnosis for eugenic and economic reasons.

(b) The promise of a perfect baby

To understand attitudes towards fetal diagnosis, it is important to consider the context in which developments are often presented. Claims often far outstrip what is possible, encouraging parents to feel that all fetal problems can be recognised and a perfect baby is (almost) ensured. Complications of the techniques and their limited application are not always made clear. The media, epidemiologist and obstetricians are generally enthusiastic about prenatal screening and very optimistic about its potential for reducing the prevalence of disability.

Many conditions cannot be diagnosed. Many of those that are diagnosed would not have survived beyond the perinatal period. Population screening is not undertaken for most conditions and, of course, much handicap arises after birth.

(c) The camel's nose

Almost daily the list of conditions that can, and are, diagnosed in pregnancy grows. Inevitably, that list now includes some conditions which many feel are not sufficiently serious to justify abortion. This is the philosphers slippery slope - or to use the arabic saying that Barbara Katz Rothmen (1987) employs - it is the camel's nose.

If you once let a camel put its nose into your tent you will soon be joined by the whole camel. There seems wide agreement that Downs syndrome and the major neural tube defects, for example, are sufficiently serious to justify the possibility of abortion. But what of less serious disorders? We know at least from one small series that in about half of these cases parents opt for abortion (Homes-Siedle, et al, 1987; see also, Canner, 1986). Should we regard that as a success; or perhaps the diagnosis should never have been made, or if made, not passed on to the parent? What of those parents who decide not to abort? Is not their knowledge of their child's chromosome situation an unnecessary emotional and social complication? Are not they likely to interpret every odd bit of behaviour or other difficulty of their child as a consequence of the extra chromosome? Are we justified in withholding a diagnosis from parents if it is of a condition we judge to be of little consequence? Perhaps we have to think in terms of lists of conditions parents would like to have and not have diagnosed that might be agreed before diagnostic procedures are started.

In Sweden, screening for antitrysin deficiency was discontinued after it was found that the identification of children led to considerable psychological reactions from some parents and prolonged disturbance of the parent-child relationship (Thelin, et al, 1985).

But the camel's nose is not simply a problem for individual parents, is there not also a danger that we may inadvertently foster an attitude that any fetus that is less than perfect should be discarded?

A camel that has already entered some tents is that of sex determination (Q.V. Levidow, 1987). Chromosomal examination allows determination of the fetal sex or this may be done through an ultrasound examination. How do we feel if parents use information about the fetal sex to influence decisions about abortion? Unless we avoid all fetal sex determination (or prevent parents getting the information) I suspect we cannot stop the sex of the fetus becoming for some, a major consideration when abortion is being considered.

(d) Who makes decisions?

One of the arguments that has been used against the development of fetal diagnosis is that it tends to put more control over reproduction in to the hands of clinicians and removes this from women and their partners. While it seems to be true that there is wide acceptance of the new techniques among women, they have not had a voice in the research policies and planning that have created the present pattern of services. They can simply take or leave what is on offer.

Often, conditions are set about who may have access to diagnostic services. The information available to women on which they make choices may be limited or it may be presented in such a way as to favour particular choices (see section on counselling).

Wendy Farrant (1985) points to a significant difference in perspective of obstetricians and those who they serve. For most women the prime goal of fetal diagnosis is reassurance about their fetus while obstetricians place priority on the diagnosis and abortion of affected fetuses. This latter concern leads some obstetricians to limit diagnosis to those who will make a prior decision to abort in the event of a positive diagnosis. The difference in perspective of provider and user of the service is illustrated by Farrant's result that while 80% of obstetricians rated the communication of a positive diagnosis as very urgent, only 33 % gave the same priority to a negative result. The same attitude leads some not to inform women at all about negative results and simply to tell them they may assume that all is well if they do not hear by a particular date. Further evidence of the differing perspectives is provided by the relative low priority given to the development of counselling services in relation to that accorded to diagnostic facilities. Such attitudes are apparent in considerations of costs and benefits of services which take no account of counselling needs.

(e) Feelings and attitudes about pregnancy

The way in which a pregnancy is experienced may be changed by diagnostic procedures. In the initial stages before the diagnostic processes are begun, a woman who knows she is going to undergo these may regard her pregnancy as tentative, to use Barbara Katz Rothman's phrase (1987). She suggests that news of the pregnancy is more likely to be kept private at this stage and women may put off wearing maternity clothes. Once the tests are complete a mother may swing in the opposite direction now seeing her fetus as a baby, naming it, spreading the news and going out to celebrate as one might after the birth. Others have commented on a bonding process between mother and fetus which they suggest can follow the seeing of the fetus on an ultrasound scan (Lumley, 1980; Rowledge, 1983; Fletcher and Evans, 1983). This may become a psychological turning point in pregnancy. Some of my informants complained that the psychological significance of the scan - which they compared to birth itself - was not recognised by those who conducted the examination.

Is it of consequence that we may have shifted some of the psychological processes that are generally associated with birth to an earlier point in pregnancy? (see Beeson, 1984; Fletcher, 1972). Perhaps not, but I feel some concern for those who may lose a baby or who give birth to a baby with significant handicaps after going through this process.

Much of the research related to diagnostic procedures has been concerned with issues of anxiety and reassurance. This work shows, not surprisingly, that before ultrasound or amniocentesis mothers in risk groups are more anxious than those facing a screening examination.

Some studies point to factors which may be associated with the level of anxiety. Robinson et al (1984), for instance, showed that women with least social support showed the highest levels of anxiety at amniocentesis. Their study also indicates that there is a greater fall after the test when results are directly communicated to the mother than when she is simply left to assume all is well if she has not heard by a particular date. Others stress the importance of the manner in which information is given (Furness, 1987; Tsoi and Hunter, 1987).

The period of waiting for results can be particularly stressful (Beeson and Goldbus, 1979; Taber and Johnsson, 1987). Farrant (1980) has called attention to the body of work which suggests a link between stress and anxiety in pregnancy and low birth weight, miscarriage and other poor outcomes. Some women in her study reported smoking more and taking tranquillizers while waiting for test results and Farrant suggests that anxiety associated with pre natal diagnosis could contribute to poor outcomes.

(f) Counselling and the family

We have already noted the low priority that is often accorded to the provision of counselling in association with programmes of fetal diagnosis. When a positive diagnosis leads to an abortion good counselling is vital (Jorgensen et al, 1985).

Researchers have raised another issue in relation to the counselling. This concerns the directiveness or otherwise of counselling about parents' decision making. It is, of course, an article of faith of genetic counsellors that they should provide information and assist parents towards their own decision, that their counselling should be non-directive. This same ethic informs counselling about whether or not to have an amniocentesis. However, research studies report that some women in the appropriate age group experience strong pressure to undergo amniocentesis and may feel poorly informed about the possible consequences (Farrant, 1985; Katz Rothman, 1987). Farrant found that after amniocentesis 24% of women were unaware of the risk of miscarriage and 86% did not know of other possible hazards. The minority who knew of possible risks for their babies had learnt about this from sources other than the person counselling them about amniocentesis. Perhaps most reavealing of all was the finding that this information was only given to women who staff were trying to persuade not to have amniocentesis because they were younger than the particular age cut off point used at the hospital in question.

In discussing counselling we must consider not simply the mother but others in her family. Decisions that are made are likely to have many repercussions for other family members. We lack systematic research.

Katz Rothman's (1987) respondents (see also Elkins et al, 1986) said that their decisions to undergo amniocentesis were discussed with their partners who either actively supported their decisions or were content to go along with them. However, a significant minority of mothers who refused the test did not discuss this decision with their partners.

I think there is an urgent need of knowledge about the family repercussions of the use of fetal diagnostic techniques so that we have a basis on which support and counselling can be offered. Informed counselling may avert some of the tragedies that I fear may otherwise lie ahead.

(g) Attitudes to the handicapped

It is a hard and continuing struggle to ensure that adequate services and support are available to the handicapped and those who care for them. Slowly attitudes have been changed and there is a much greater degree of acceptance than existed a generation ago. Will fetal diagnosis change the situation? Some fear it will because conditions that are screened for have become avoidable. But what of the affected child born to parents who decided against a screening examination - or to those who began their antenatal care at a point after that at which screening and abortion are possible? Are such parents going to feel a new responsibility and guilt for producing an affected child? As forms of handicap became avoidable in this sense, is society at large going to place (even) less priority on services for them? As Farrant (1985) has pointed out, the DHSS has not been slow in making the case,

> "because caring for the handicapped can impose great burdens on our society, the prevention of handicap.....in addition to its other benefits may save money"
>
> (DHSS, 1977, quoted in Farrant, 1985)

(h) Social class and ethnic differences

In discussing social class and ethnic differences, we seem to be faced with two conflicting concerns. The first assumes that the inverse care law (Tudor Hart,.....) will apply to screening and prenatal diagnosis, so it will be the articulate, vocal and politically powerful that will use the new techniques most effectively and for whom there will be the most marked fall in births of affected children. This would mean that an increasing burden of caring for handicapped children would fall on those with fewest resources and who are least able to press for better services and support. That does seem to be a road down which we may be travelling. Furthermore, while some minorities such as the Cypriot population in London, may have been well served in respect of screening for beta thallasemia, this appears not to be the case for

all communities that have a relatively high frequency of the gene (see Donovan, 1983). If the example of sickle cell anaemia is anything to go on (Prasher, Anionwu and Brozovic, 1985) some minority communities may find it difficult to get adequate screening, counselling and supportive services.

Conclusions

This paper was written as an introduction to a series of discussions so it would be out of place to attempt any overall summary. I have attempted to highlight the potential problems as they appear to a social scientist. But I would make one final point. Of the enormous amount of research that has been carried out in connection with the new techniques, very little has been attempted to see things from the point of view of those for whom, in theory at least, the techniques have been devised. As Daker and Bobrow (1987) state, there is still a 'regrettable dearth of good quality psychological and sociological research' in the field. There are too many examples in the history of medicine of technological research and development running far ahead of knowledge of how to use and deploy what is available. Despite the warnings, this field may be going to provide another example - I hope not.

GENETIC AND CONGENITAL DISORDERS

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At least 1% of all live babies have a disorder inherited in a simple Mendelian fashion that is manifest at birth, or will develop later. If one includes multifactorial conditions where there are substantial genetic influences, the figure rises to 2-5%. It has been estimated that genetic causes account for 75% of all severe handicapping disorders in childhood, and increasingly these children are surviving into adult life. Genetic factors can also greatly influence the susceptibility, or resistance, to many of the chronic mental and physical illnesses of later life.

The term congenital just means present before or at birth and does not necessarily imply that genetic influences are involved, although they often are. In simple Mendelian inheritance the abnormality or failing health in early life is determined at conception, the course of events altered little by environmental factors. The mutation that is disrupting gene function is the cause of the disorder. In the same way an extra 21 chromosome is the cause of Down's syndrome. In the common congenital malformations like spina bifida and congenital heart defects there is no single cause. The malformations arise as a result of the combination of certain genes that are inherited plus other non-inherited factors, all largely unknown. The latter can be an environmental influence (as far as the fetus is concerned) such as maternal diabetes mellitus, or a post conceptional event such as monozygotic twinning which is a known contributory factor in the cause of congenital heart defects.

The term multifactorial causation (multifactorial inheritance) implies that overall there is a combination of several genetic and non-genetic factors, but not that the same combination always occurs in every case. Spina bifida in one fetus may be due to a combination of genetic factors whilst in another

environmental influences may predominate. Unlike Mendelian inheritance where our understanding of the mechanism involved allows us to say that all healthy couples with one child with β-thalassaemia or cystic fibrosis face a 25% risk of the next baby being affected, in multifactorial inheritance we can only give an average recurrence risk figure derived from empirical observations on large numbers of families (Table 1).

Simple Mendelian inheritance is outlined in the 'Primer' provided and Tables 2,3 and 4 give the incidence of the commoner autosomal dominant, autosomal recessive and X-linked disorders in the British population. There are literally thousands of other Mendelian disorders that although individually rare in aggregate represent a huge amount of suffering.

The first practical problem for the affected family, common to all medicine, is making a correct diagnosis as early as possible. Thereafter other family members can be advised as to any genetic risks. In practice, the very rare disorders are often misdiagnosed, many families are not advised of the genetic risks, and it would be wrong to assume that people will volunteer information about disorders in relatives. In autosomal dominant and X-linked disorders an effective first screen as to who is at risk can be provided by taking the family history. This simple procedure which should be carried out for everyone reaching a fertile age is sadly neglected. In the past, I suspect many physicians were discouraged by not knowing what to do when something cropped up. In how much detail should some vague diagnosis be pursued? What tests if any are available to clarify the risk in an individual family member? If one probes too deeply will it stir up trouble in the family? Nowadays Regional genetic counselling services should be in a position to provide the necessary support and expertise. However, dominant and X-linked disorders may also turn up 'out of the blue' either because the affected person (or their mother in X-linked recessive disorders) represents a new

mutation, or just because of small family size. Autosomal recessive inheritance by its very nature, results in the vast majority of affected children being the first in the family. Prompt diagnosis is essential if couples are to be forwarned about risks to further children, but the antecedent family history rarely provides a clue.

Where there is a family history of an autosomal dominant or X-linked disease, genetic prediction (carrier detection or prenatal diagnosis) may be possible, and increasingly the strategy used is gene tracking. This approach is usually possible once the disease gene locus has been mapped to a particular chromosomal region for which there are 'DNA markers'. Whilst not detecting the mutation itself, the DNA probes used can detect naturally occuring variations in neighbouring DNA sequences that co-inherit with the disease.

Gene tracking can also be used in autosomal recessive disorders but only after the couple have had an affected child. For this reason different approaches are needed for carrier detection of autosomal recessive mutations.

Chromosomal disorders involve genetic abnormalities that are visible by light microscopy. Changes in chromosome number such as trisomy 21 (Down's syndrome) usually arise as a result of errors in meiosis in either parent who themselves have no chromosome abnormality or rearrangement. Indeed, the vast majority of babies with chromosomal defects represent 'new mutations'. The number reaching term is only a fraction of those conceived. Babies with a chromosomal trisomy are more commonly born to older women but the actual risks (around 1 in 80 at 40 years) is nowhere near the risks faced in Mendelian inheritance. However, there are inherited chromosome abnormalities in the form of chromosome translocations. About 1 in 500 of the population carry a balanced rearrangement between two different chromosomes and many of these people face about a 10% chance of producing a severely handicapped child with

an unbalanced chromosome complement.

The rarer small structural abnormalities involving single chromosomes such as visible deletions probably represent the tip of an iceberg of deletions and rearrangements lying beyond the resolution of light microscopy. Here chromosomal abnormality merges with Mendelian inheritance.

The common form of mental retardation associated with a fragile site (an unstainable gap or constriction) near the tip of the long arm of the X - the fragile X syndrome is an example.

In terms of detecting those families at risk of <u>transmitting</u> a chromosomal defect including the fragile X syndrome, emphasis must be placed on examining the chromosomes (including where appropriate, studies to reveal fragile sites) in all mentally retarded individuals and babies with multiple malformations.

Defining who faces a high risk of a handicapping disorder in their offspring is of course, only part of the equation as far as the family are concerned. They would like to know how severely affected the child would be in their particular case. Usually all that one can do is indicate the range and average severity of the condition, list the possible complications and the chance of them occuring, and try to give a balanced view of the effect of therapy or other forms of intervention. Occasionally fetal examination by ultrasound can reveal complications that adversely effect the prognosis, such as early hydrocephalus with spina bifida or atrio-ventricular septal heart defect in Down's syndrome.

Table 1

EMPIRICAL RISKS (PERCENTAGES) FOR SOME COMMON CONGENITAL MALFORMATIONS IN BRITAIN

Disorder	Population incidence	Normal parents having a second affected child	Normal parents having a third affected child	Affected parent having an affected child
Cleft lip ± cleft palate	0.10	4	14	4
Spina bifida/ anencephaly	0.3-0.7	3-5	10-12	3-4
Congenital heart defects	0.8	2-4	~10	5-6

Table 2 Estimates of birth frequencies of some more common dominant conditions (symptomatic and asymptomatic) in Britain per 1000 live births

System	Disorder	Frequency
Nervous system	Huntington's chorea	0.5
	Neurofibromatosis	0.3
	Myotonic dystrophy	0.2
	Hereditary motor and sensory neuropathy (Charcot–Marie–Tooth disease)	0.2
Intestines	Multiple polyposis coli	0.1
Kidney	Polycystic disease of the kidneys	0.8
Skeleton	Diaphysial aclasis	0.5
Sight	Dominant forms of blindness	0.1
Hearing	Dominant forms of early childhood onset deafness	0.1
	Dominant otosclerosis (adult onset, severe)	1.0
Circulation	Monogenic hypercholesterolaemia	2.0
Teeth	Dentinogenesis imperfecta	0.1
Blood	Congenital spherocytosis	0.2

Table 3 Estimates of birth frequencies of some more common recessive conditions in Britain per 1000 live births

System	Disorder	Frequency
Metabolism	Cystic fibrosis	0.5
	Phenylketonuria classical	0.1
Nervous system	Neurogenic muscle atrophies	0.1
Red blood cells	Sickle-cell anaemia	0.1 *
Endocrine glands	Adrenal hyperplasias	0.1
Hearing	Severe congenital deafness	0.2
Sight	Recessive forms of blindness	0.1
Mental retardation severe	Non-specific recessive forms	0.5

Table 4 Estimate of birth frequency in males of the more common X-linked conditions in Britain per 1000 live births

System	Disorder	Frequency
Locomotor system	Duchenne muscular dystrophy	0.25
Blood clotting	Haemophilia A	0.1
Skin	Ichthyosis	0.1
Mental retardation	Fragile X syndrome	0.75

* Confined largely to people of Afro-Caribbean origin where the incidence is about 5/1000

THE EPIDEMIOLOGY PRINCIPLES OF SCREENING

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"Screening represents a radical departure from traditional medicine, for it is usually concerned with the detection of disorders at an asymptomatic stage which cannot, therefore, have prompted the patient to seek medical attention; indeed it often involves seeking out such asymptomatic individuals among people who are not receiving any type of medical attention. It is tempting to believe that the early detection of disease is a good thing and an end in itself, forgetting that the identification of either trivial or untreatable conditions may cause anxiety with no useful result. Screening must, therefore, be concerned with the prevention of disease and the recognition that it is only worthwhile screening for disorders which lend themselves to effective intervention."[1]

Screening has been defined as: "... the identification, among apparently healthy individuals, of those who are sufficiently at risk of a specific disorder to justify a subsequent diagnostic test or procedure, or in certain circumstances, direct preventive action."[1]

Five important implications arise from this definition:

1. The screening 'test' which separates an at risk group from the general population may involve no more than a simple enquiry such as asking a woman her age when screening for Down's syndrome or asking whether an individual has an affected close relative when identifying carriers of certain genetic disorders.

2. Screening seeks to identify subjects who are at risk of a specific disorder. The disorder should be well defined and distinct from the screening test. The tendency to regard being at risk of a disorder as having a disorder itself should be avoided. For example, measuring a person's blood pressure should not be regarded as a screening procedure for 'hypertension'. The circularity confuses the issue and makes the evaluation of screening impossible. Sometimes the distinction between test and disorder is difficult to make because a positive screening test result will, on ethical grounds, always lead to treatment before the disorder occurs. The measurement of neonatal T_4 or TSH levels as a screening for cretinism provides an extreme example. A positive result will always lead to treatment to prevent the development of cretinism. In such circumstances distinguishing test from disorder is impossible, but awareness of the problem can avoid obvious errors in the evaluation of screening.

3. Assessing those who are sufficiently at risk of a specific disorder to justify further action involves striking a balance in the population concerned between (i) the severity of the disorder, its natural history and its prevalence in the community on the one hand, and (ii) the availability, acceptability and safety of an effective method of screening, diagnosis and treatment.

4. The definition of screening is based largely on the fact that it is the purpose for which a procedure is carried out that qualifies it as screening. It is not the test itself that qualifies it as a screening test.

5. Screening tests, unlike clinical diagnostic tests, are applied to apparently healthy individuals and this raises special ethical considerations. In ordinary clinical practice the physician's obligation is to treat the patient in the best way he can, even if there is incomplete knowledge about the disease or its remedy. In screening there is an obligation not to initiate any action unless the full consequences of doing so are known and there is an effective remedy available.

To assess the performance of a screening test, two questions need to be asked.

1. To what extent can the test discriminate affected from unaffected individuals?
2. What is the chance that those who have positive results are affected?

The first question is answered by determining the detection rate (DR) (sensitivity) and the false-positive rate (FPR) (one minus specificity) of the screening test. The second question is answered by determining the odds of being affected given a positive result (OAP). The definitions of DR, FPR and OAP are given in the Annex.

A convenient way to illustrate the performance of screening tests is to construct a flow diagram, starting with, say, 100,000 individuals being screened. The first step is to divide these 100,000 individuals into those who are affected and those who are unaffected. Figure 1 illustrates such a flow chart for a disorder with a prevalence of 2:1000 with the use of a screening test with a DR of 80% and a FPR of 3%. In the example the OAP is 160:3000 or 1:19 (5%). The prevalence of the disorder has a marked effect on the performance of screening; if the prevalence of the disorsder were 1:1000 it is easy to see that the OAP would be reduced to 1:38 with no change in the DR or FPR. Figure 2 shows the effect of introducing a second screening test and then a diagnostic test to the example in Figure 1. Before any screening test is introduced such a flow chart should be constructed. If this cannot be done because of lack of data, the appropriate information would need to be sought before screening is introduced.

Constructing a flow diagram in this way involves making a decision as to whether a test result is positive or negative. For qualitative (or categorical) tests, such as cervical smear tests, this is straightforward, but for quantitative tests, such as maternal serum AFP measurement in the screening for neural tube defects, a decision needs to be taken on what cut-off level should be adopted that distinguishes positive from negative results. This can be done by constructing a frequency distribution showing the percentage of affected and unaffected individuals according to increasing values of the screening variable. Figure 3 shows such distributions and an arbitrary cut-off level (A) at 6 units of the screening variable. DR is given by the area under the affected curve to the right of the cut-off level (A); FPR is given by the area under the unaffected curve to the right of the same cut-off level. The ratio, DR:FPR, is the likelihood ratio. This is the factor by which the background prevalence (expressed as an odds) is multiplied to yield the OAP. The use of the likelihood ratio in this way permits the calculation of OAP without constructing a flow diagram. Figure 4 illustrates the calculation using a higher cut-off level (B) associated with a DR of 80% and an FPR of 0.5%.

It is important to note that there is usually no 'natural' cut-off level that should be automatically adopted for a particular screening test since there is usually overlap beween the distribution of values for affected and unaffected individuals; moving the cut-off level to reduce the false-positive rate will automatically reduce the detection rate. Only if the overlap between the distributions is negligible will the cut-off level be obvious.

For a particular individual with a particular screening result, OAP is given by the likelihood ratio for <u>that</u> individual times the background prevalence. The likelihood ratio at a particular screening value is the ratio of the heights of the two overlapping curves at a given screening value. While those responsible for planning screening programmes are mainly interested in the OAP for <u>all</u> those with positive results, those reponsible for counselling individuals need to know the OAP for the particular individual.

The costs and benefits of screening can be considered both in financial and medical terms. The <u>financial</u> costs and benefits are reasonably easy to estimate by constructing a balance sheet along the lines shown in Table I. For most screening programmes the total cost will be influenced mainly by the cost of the initial screening test so that, for screening to be cost effective, the test must be simple and economical. Estimating the <u>medical</u> costs and benefits is not straightforward because it usually involves the comparison of incommensurables. For example, how many miscarriages induced by amniocentesis are acceptable in relation to the prevention of one handicapped child? It is inappropriate to asssume automatically that one fetus lost through the trauma of amniocentesis is equal to, say, the identification and termination of one pregnancy associated with Down's syndrome.

It is useful to have a checklist of criteria or requirements that need to be satisfied in judging whether a particular screening programme is worthwhile. Table II shows the eight requirements for a worthwhile screening programme specified in Antenatal and Neonatal Screening.[1] To this list of requirements two more can be added, namely, the appointment of an identifiable and accountable person who would be responsible for the running of the screening programme and the setting up of a system for monitoring the effectiveness of the programme. Neither are requirements in quite the same sense as the original eight but practice has shown that they are necessary for screening to be successful and for this to be determined objectively.

"During the 1970s there was much discussion about the promise of preventive medicine through antenatal and neonatal screening. But though there has been progress the application of knowledge has been incomplete and sometimes ineffective. One of the challenges of the next decade will be to organise health services so that screening programmes are well chosen and effectively applied in the community."[1]

REFERENCE

NJ Wald (ed). Antenatal and Neonatal Screening, Oxford, Oxford University Press, 1984.

ANNEX

The detection rate (DR) is the proportion of affected individuals yielding a positive result. For example if there are 100 affected individuals and 80 of these are positive, the detection rate would be 80%.

The false-positive rate (FPR) is the proportion of unaffected individuals yielding a positve result. For example if there were 100 unaffected individuals and 3 of these are positive the false-positive rate would be 3%.

The DR and FPR do not depend on the prevalence of the disorder being screened for.

The odds of being affected given a positive result (OAP) is the ratio of the number of true positives to the number of false positives. For example if there are 100 positives, of which 80 are affected and 20 are not, the OAP is 80:20 or 4:1.

The OAP does not depend on the prevalence of the disorder being screened for.

NB. OAP expressed as a probability is known as the predictive value positive (PVP).* The performance of a screening test is determined by three parameters only, two concerned with the test itself (DR and FPR) and one with the disorder (the prevalence). All three determine the OAP.

* The PVP in our example is 80/100 or 80%. There are reasons for preferring the use of OAP to the use PVP. OAPs are numerically easier to handle and provide a better indication of the relative performance of tests. For example a test that is associated with 90 affected subjects out of 100 positives would yield an OAP of 90:10 or 9:1 - about twice as 'good' as the 4:1 odds in our example above. The equivalent PVP is 90% instead of 80% concealing the size of the increase in performance.

Table I.

Costs and benefits: Financial

Construct a balance sheet of costs and savings

Estimate

(i) cost of screening 1000 individuals
(ii) number of cases detected per 1000 screenees
(iii) saving per case detected
(iv) cost per case detected
(v) saving/cost ratio

NB Total cost will usually be dominated by the cost of initial screening test so this must be simple and economical

Table II

Requirements for a worthwhile screening programme

	Aspect	Requirement
1.	Disorder	Well defined
2.	Prevalence	Known
3.	Natural history	Medically important disorder for which there is an effective remedy available
4.	Financial	Cost effective
5.	Facilities	Available or easily installed
6.	Ethical	Procedures following a positive result are generally agreed and acceptable both to the screening authorities and to the patients
7.	Test	Simple, and safe
8.	Test performance	Distributions of test values in affected and unaffected individuals known, extent of overlap sufficiently small, and a suitable cut-off level defined

Figure 1. Example of a flow diagram illustrating the effects of screening for a disorder with a prevalence of 2:1000. The screening test has a detection rate of 80% and false-positive rate of 3%.

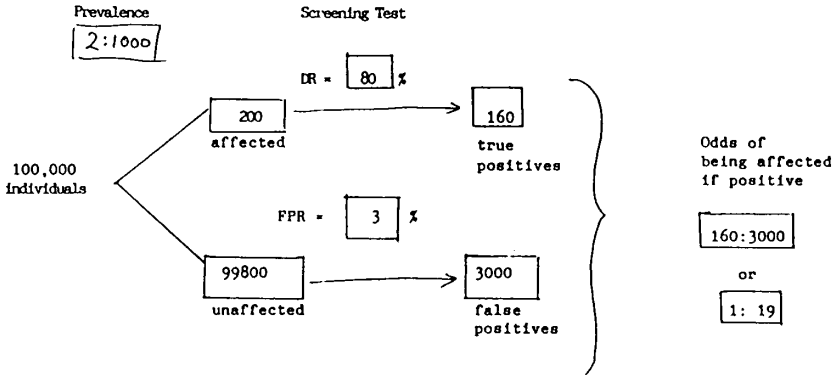


Figure 2. Extending the flow diagram illustrated in Figure 1 to show the effect of adding a second screening test and a diagnostic test.

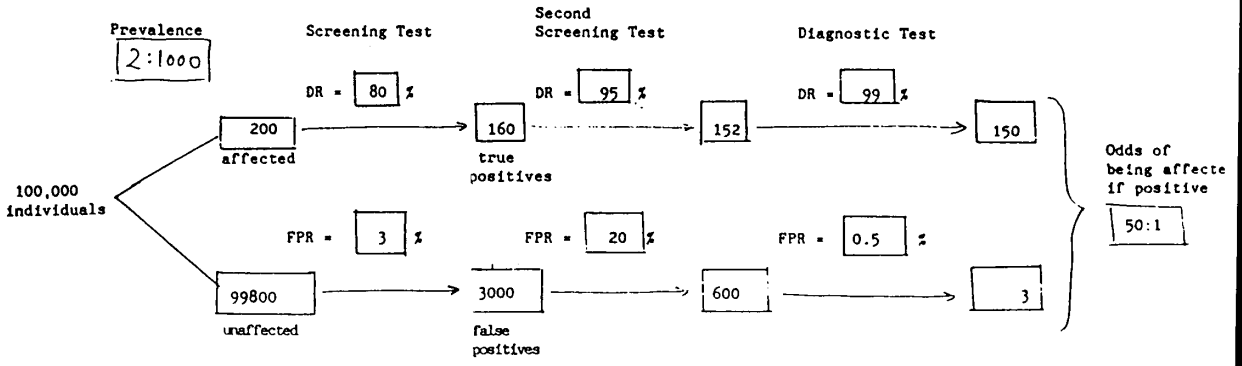
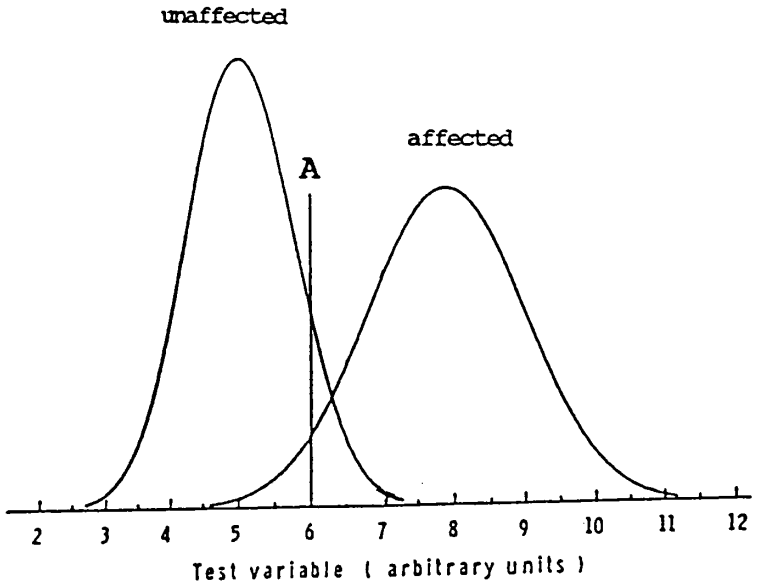


Figure 3. Relative frequency distribution of a test variable in affected and unaffected individuals: the effect of using a cut-off level 'A'.



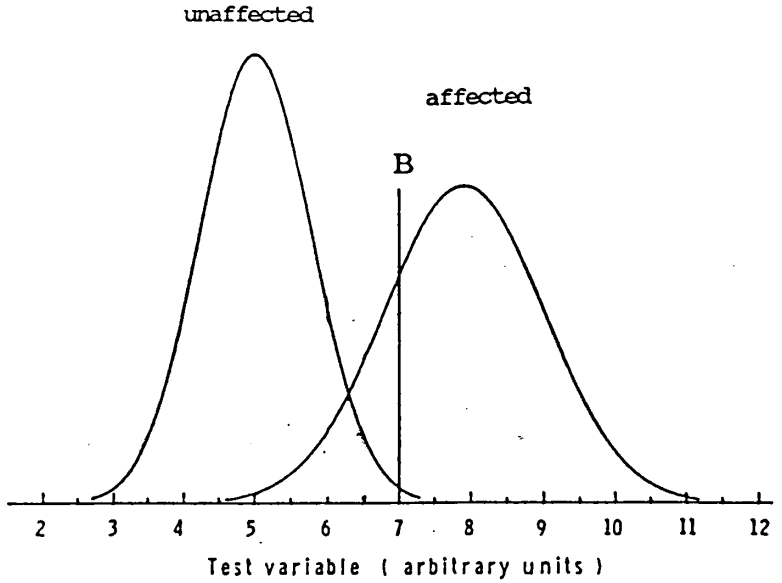
$$\frac{DR}{FPR} = \frac{95\%}{10\%} = 9.5 = LR$$

OAP = LR x Background prevalence

= 9.5 x 2:1000

= 19:1000

Figure 4. The effect on screening of using a 'higher' cut-off level 'B' with the same distributions illustrated in Figure 3.



$$\frac{DR}{FPR} = \frac{80\%}{0.5\%} = 160 = LR$$

OAP = LR x Background prevalence

= 160 x 2:1000

= 320:1000

24%

OBSTETRIC TECHNIQUES

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Obstetric techniques for prenatal diagnosis can be divided into non-invasive imaging techniques (of which ultrasonography is paramount) and invasive sampling methods. The latter include amniocentesis, chorion villus biopsy and sampling of fetal blood and other tissues such as skin and liver. Some aspects of these will briefly be dealt with in turn.

Ultrasonography

This has several important roles to play. (a) In the most skilled hands, the best equipment available today is capable of revealing the internal anatomy of the fetus in considerable detail, so that many malformations can be diagnosed. Such an examination is usually performed at 18-20 weeks' gestation. (b) Ultrasonography provides essential information on whether the fetus is alive, how many fetuses there are, and the gestational age can also be confirmed. (c) It is a sine qua non for guidance of all the invasive procedures. (d) Recently developed Doppler equipment is being used to investigate functional aspects of the fetal circulation.

There is no evidence that diagnostic ultrasound is harmful. Diagnostic errors do occur, as with any other investigation, but the incidence can be remarkably low. All ultrasound departments should continuously audit their performance and further evaluation of ultrasonography as a screening technique is required.

Amniocentesis

This was introduced nearly 20 years ago and is the most widely used invasive technique. Amniotic fluid is obtained by a needle passed transabdominally, with ultrasound guidance, and usually at 16 weeks. The investigations that can be performed include chromosome analysis, biochemical and DNA studies and alphafetoprotein (AFP) and acetylcholinesterase estimation. The commonest indication is fetal chromosome analysis in mothers at increased risk of bearing a fetus with Down syndrome, i.e. those aged 37 or more. The main complication is fetal loss due to miscarriage and the risk of this is increased by 1% over the ackground.

Chorion Villus Biopsy

CVB was introduced more recently (1982) and is being used increasingly. In theory, it could replace amniocentesis, but is unlikely to do so completely. Its greatest advantage is that it can be performed in the first trimester, usually about 10 weeks. A number of techniques are available, both transcervical and transabdominal. The range of possible investigations is similar to amniocentesis, i.e. chromosomal, biochemical and DNA analysis, but AFP cannot be measured and hence, it is of no value for the detection of neural tube defects. Chromosome studies are quicker than on amniotic fluid and DNA analysis is easier because more DNA is obtained.

The risks are not yet precisely known but the fetal loss rate is probably increased by 2%. At present, it is used mainly for high-risk mothers with a genetic history, e.g. thalassaemia, cystic fibrosis. It is not yet routinely available for women over 37 years because trials are still being carried out and the facilties are not widespread.

Fetal Blood Sampling

For 10 years, fetal blood was obtained by fetoscopy, but recent improvements in ultrasound equipment have led to a needle-guided technique. The umbilical vein at the placental insertion of the cord is usually chosen, but other sites are possible. The procedure can be performed between about 18 weeks and term. The main indications are (a) rapid karyotyping from fetal lymphocytes, most commonly when a fetus has been found to have a malformation; (b) the assessment of fetal oxygenation by estimation of pH and PO2 in cases of fetal growth retardation, and (c) the assessment of fetal anaemia in haemolytic disease (usually still due to rhesus isoimmunisation). In these circumstances, fetal transfusions can also be given. The risk of fetal loss in experienced centres is only 1-2%

Other Fetal Tissues

Diagnostic samples of fetal skin and liver may be taken in a variety of severe genetic diseases and fetal tumours can be biopsied. These procedures can be fetoscopic, but more recently have also become ultrasound-guided.

NEURAL TUBE DEFECTS AND DOWNS SYNDROME A SUCCESS AND A FAILURE

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The two most common conditions for which prenatal screening is available are neural tube defects and Down's syndrome. As judged by one criterion of success, namely the avoidance of affected livebirths, the neural tube defect screening programme has been highly effective while the screening programme for Down's syndrome has made only a small impact. In the most effective programmes, neural tube defect births have been reduced by 75% while for Down's syndrome births the figure is between 15-20%. The key to the difference is the acceptability of the screening test, and as both methods are quite different it seems appropriate to discuss each in turn.

A neural tube defect results from failure of the embryonic central nervous system, the neural crest, to form into a neural tube. If it fails to close at the tail end, the spinal cord is defective and spina bifida results. If it fails to close at the head end, anencephaly results. The causes of both are unknown but likely to be identical, as the occurrence of one in a family predisposes to either in subsequent offspring. Most commonly both defects fail to be covered by skin as the fetus develops so that fetal blood proteins, particularly alphafetoprotein (AFP) leak out into the amniotic fluid. Excessive amniotic AFP is thus the basic diagnostic test for open neural tube defects. Some of this excessive AFP is absorbed into the mothers circulation, where it can be measured by a simple blood test. The maternal serum AFP is the basic screening test for neural tube defects. The test is positive in about 85% of 16-20 week pregnancies affected by open neural tube defect, and is acceptable to over 90% of mothers. In practice, about 75-80% of mothers use the test, the remainder are either too late in pregnancy or are not offered the test by their doctors; a few (less than 7%) decline the test because they have moral objections to prenatal diagnosis.

False-negative maternal serum AFP results occur in about 15% of affected pregnancies, but these are usually either small defects or closed defects. False-positive results are uncommon and may be due to fetal blood contamination. However, all positive results require confirmation and this invariably means a detailed ultrasound scan, which nowadays almost always reveals the neural tube defect or a less common abnormality. If no abnormality is seen, amniocentesis is usually advised so that the amniotic fluid can be tested for AFP and acetylcholinesterase. If both are positive, a neural tube defect is present, for false positive results of these amniotic tests are almost unknown. A negative amniotic AFP test should reassure the mother.

The best AFP screening programmes are those that provide full information to the mother, that provide the laboratory results quickly and have good liaison between laboratory, obstetrician and patient. A positive AFP result engenders extreme anxiety in the mother and it is essential that there is good communication, rapid recall for confirmatory testing and sympathetic counselling. No mother should have blood taken for AFP without understanding what it is for, and without giving consent. She is free to refuse further testing and may decline termination of pregnancy at any stage.

Table I gives details of the West of Scotland screening programme over ten years. During that period the overall rate of neural tube defects have fallen from about 5 per 1000 to about 2 per 1000, including 0.5 per thousand affected live births (Fig. 1). Some of this reduction seems to be due to early ultrasound diagnosis and selective termination of affected pregnancies. It is often suggested that an improved standard of living including diet is responsible for the fall in rate. The preventative role of vitamin supplementation to the diet of women at higher risk (1 in 20-25) because of a previous affected child, has been much debated in recent years. However, the case control studies of Smithies & collaborators have been criticised as being subject to

bias, and the MRC have launched a randomised trial of vitamin-supplementation to decide the issue. Regrettably, the initiative is being jeopardised by well-meaning lobbyists who do not appreciate the need for a trial, and who have persuaded the Committee on Safety of Medicines, to authorise the sale on prescription of certain multivitamin preparations for the prevention of recurrence of neural tube defeects. This decision pre-empts the conclusions of the randomised trial and makes recruitment into the trial much more difficult.

Screening for Down's syndrome (mongolism) is a different matter because it requires fetal chromosome analysis of cultured amniotic fluid cells or of chorion villus (placental) samples. Both involve minor operative procedures under the guidance of obstetric ultrasound. Fetal chromosome analysis is required to recognise the additional chromosome material in Down's syndrome cells. In 95% of cases this is an extra chromosome resulting from an accident of cell division usually occurring during the formation of the mother's egg. Such events occur more frequently in older women, and the risks become unacceptable to most women when they reach 35 years of age. About 6-7% of pregnant women are in this category and approximately 30% of Down's syndrome children are born to such mothers. However, only 30-40% of these women have their pregnancies tested for Down's syndrome and in consequence only 15-20% of affected pregnancies are avoided (Table II). Many older mothers are not offered fetal chromosome analysis, either because the obstetrician does not believe that the risk of abortion (0.5 - 1.0%) justifies it, or because the mother attends the antenatal clinic too late for amniocentesis. In the best ordered programmes, the mother is counselled about the risk of Down's in relation to her age and then makes a decision about whether or not to have her pregnancy tested.

Fetal chromosome analysis is also capable of detecting maternal age dependent chromosomal syndromes other than Down's syndrome. Some are very severe abnormalities, such as trisomy 18 and trisomy 13, but others are associated with much less disability, for example the XXY and XXX syndromes. It is wise to mention the occurrence of these conditions when counselling older mothers prior to prenatal diagnosis, so that the couple can reach the correct decision about whether or not to continue the pregnancy should the fetus be found to be affected.

While it is not possible to diagnose Down's syndrome by ultrasonic examination, fetuses with chromosomal syndromes tend to have features which can alert the experienced ultrasonographer. These include small head to body ratios, evidence of intrauterine growth retardation, congenital heart disease and certain intestinal malformations. In the last two years, a more promising adjunct to the identification of fetuses at risk has emerged following the observation that Down's syndrome pregnancies are associated with low maternal serum AFP results. It is now possible to combine the risk associated with maternal age and the risk according to low serum AFP to produce a more accurate estimate of the probability that a given pregnancy is affected. It would be possible to offer amniocentesis and fetal chromosome analysis to all women over 26 years if the risk exceeds 1 in 250. Such a practice could reduce Down's syndrome livebirths by about 40%. There remains the hope that better biochemical markers in maternal serum will be discovered soon which will allow more effective screening for Down's syndrome than is currently possible.

Table 1.

WEST OF SCOTLAND MSAFP PROGRAMME: PROPORTION OF NTD - AFFECTED BIRTHS AVOIDED

EXPECTED YEAR OF CONFINEMENT	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985
SCREENING PERIOD	1-4	5-8	9-12	13-16	17-20	21-24	25-28	29-32	33-36	37-40
TOTAL PREGNANCIES	28549†	27782 †	35081	37714	37651	38201	35784	36013	35456	37974
PREGNANCIES SCREENED	6122	11585	17220	22929	26320	27889	28406	27510	26423	28094
PROPORTION SCREENED (%)	21.4	41.7	49.1	60.8	69.9	73.0	79.4	76.4	74.5	74.0
NTD TERMI-NATIONS	29	43	63	87	75	107	95	73	70	61
*ALL OTHER NTDs	109	109	119	106	80	78	58	38	35	21
TOTAL NTDs	138	152	182	193	155	185	153	111	106	82
NTD RATE PER THOUSAND	4.8	5.5	5.2	5.1	4.1	4.8	4.3	3.2	3.0	2.1
PROPORTION TERMINATED (%)	21.0	28.3	34.6	45.1	48.4	57.8	62.1	65.8	66.0	74.4

* Other NTDs includes 30 elective continuations of pregnancy. Occult lesions are not included.

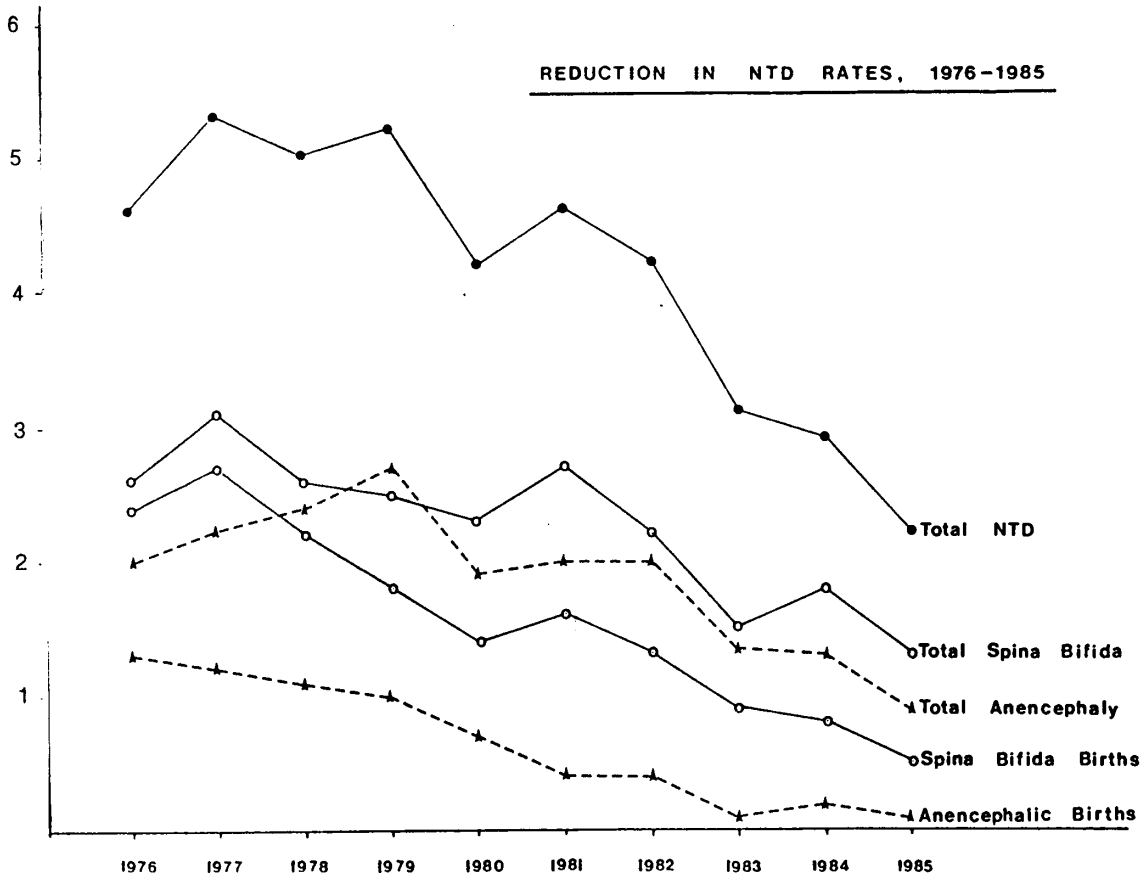
† Excludes Lanarkshire

Table 2.

WEST OF SCOTLAND PRENATAL DIAGNOSIS PROGRAMME: IMPACT ON DOWN'S SYNDROME

	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985
TOTAL BIRTHS	35225	33984	35018	37714	37651	38201	35784	36013	35853	35000
NUMBER MATERNAL AGE ≥ 35 YEARS	2231	2095	1963	2285	2175	2262	2213	2285	2243	2100
PERCENT	6.3	6.2	5.6	6.1	5.8	5.9	6.2	6.3	6.3	6.0
NUMBER SCREENED	185	391	440	478	546	642	674	702		.
PERCENT ≥ 35 YEARS	7.6	18.7	22.4	20.9	25.1	28.4	30.5	30.7	.	.
TRISOMY 21 TERMINATIONS	3	4	1	8	4	3	12	11	8	7
TRISOMY 21 LIVE BIRTHS	45	39	42	41	33	37	21	47	29	37
TERMINATIONS MINUS THIRD	2	3	1	6	3	2	8	8	5	5
TOTAL TRISOMY 21	47	42	43	47	36	39	29	55	34	42
RATE PER 1,000	1.3	1.2	1.2	1.2	1.0	1.0	0.8	1.6	1.0	1.2
PERCENT TRISOMY 21 AVOIDED	4.3	7.1	2.3	12.8	8.3	5.1	27.6	14.5	14.7	11.9

(Updated from Ferguson-Smith, 1983)


REDUCTION IN NTD RATES, 1976-1985
6
5
4
3
2
1
1976
1977
1978
1979
1980
1981
1982
1983
1984
1985
Total NTD
Total Spina Bifida
Total Anencephaly
Spina Bifida Births
Anencephalic Births

AN OBSTERIC VIEW OF POPULATION SCREENING PROGRAMMES

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There is inevitably a gap between the theoretical and use effectiveness of any intervention procedure. The South Wales Anencephaly Spina Bifida Group was established to assess the feasibility, acceptability and effectiveness of screening for neural tube defect under 'field' conditions in a district with a high incidence of neural tube defect. A detailed financial evaluation was also made. The survey covered nearly 16000 deliveries and included 68 open neural tube defects. A clear protocol was established but not necessarily adhered to by the participants. However, careful supervision of varying clinical practices was closely monitored.

Twenty five steps in the screening procedures were identified and monitored with a view to optimising the service. The overall detection and termination rate for open spina bifida was 54%, far short of the theoretical target. Of those patients screened 73% of open neural tube defects were detected and terminated.

Failure to Screen

The main reason for non admission to the screening programme was late attendance at a booking clinic (20%). Approximately one third of these were late in seeing any doctor, in one third of cases there was delay in the general practitioner referring the mother and in the remainder there were a variety of administrative delays. A publicity campaign appeared to have minimal effect but considerable improvement could be achieved by prompter referral and administrative improvements.

The general policy was for mothers to opt in rather than opt out and suitable literature was made available in GP's surgeries as well as the hospital clinics but usage in general practice was very disappointing. Only a few patients opted out of the programme and only one declined termination following diagnosis of neural tube defect.

Blood Sampling

This was done solely at hospital clinics to ensure confirmation of gestational age and to clearly define clinical responsibility. There were significant errors in menstrual dates in approximately 20% patients and 20% samples received in the laboratory had been taken outside the agreed gestational age range.

Assay and Turn Round Time

Automated assay minimised the laboratory phase but, because of the short time available, special arrangements had to be made for transport of samples and for rapid communication of results. This imposed a significant additional burden on laboratory and clinic staff, especially over holiday periods.

Abnormal Results

The further management of patients with abnormal results normally was undertaken at a central assessment clinic which provides counselling, ultrasound and amniocentesis facilities.

Ultrasound

Ultrasound has played an increasing role in the detection of neural tube defects, with detection rates as high as that achieved by biochemnical tests. However, such results are based on detailed scanning of identified high risk groups and the 'vigilance decrement' which occurs with dilution of abnormalities might lead to a poorer detection rate if ultrasound was used as a total screening policy. Nevertheless, many other congenital abnormalities, often amenable to neonatal treatment, have been detected as a bonus.

Psychological Aspects

Anxiety levels have been assessed by the STAI test at various stages in the screening procedure. An abnormal serum result causes a high degree of anxiey. The protocol required that all mothers be informed positively of the result, whether it be normal or abnormal, either by attendance at the clinic, or by letter or by a home visit. Approximately half the participants did not adhere to this protocol for normal results and in such cases the mother had been told to assume that the test was normal if she did not hear from the hospital within one week. There was a significant difference in the anxiety levels of mothers two weeks after amniocentesis, depending on which procedure had been adopted. Positively informed mothers had lost their anxiety whereas the mothers told to assume the result was mormal remained anxious. In a further group of mothers in whom amniocentesis had been found unnecessary because of reassessment of gestational age and interpretation of the AFP result also had some residual anxiety. The importance of personal support was also reflected in anxiety. Those mothers who had good family support and good social contacts were far less anxious than those with poor support.

Monitoring of Results

Laboratory quality control is standard practice and caused no problems. Effective clinical monitoring of the service is more difficult on a large scale and requires additional resources for which funding may not be readily available. Standard hospital returns and birth registrations were found to be too unreliable to detect any but major deficiencies in the service. In particular, erroneous terminations of normal pregnacies may easily go undetected in a regional monitoring system, principally because abortion returns only require the indication for termination to be given and if this is under clause 4 there is no requirement to state whether or not the suspected abnormality was in fact confirmed.

Cost Benefits

The South Wales data has been analysed to assess the effects of various options and strategies in relation to major gains and losses. The figures presented, whilst based on factual data in one district, are only intended as a model on which other centres can base their own calculations and should not be extrapolated to give national estimates.

The major financial determinant in terms of preventing the birth of an affected child is the population prevalence of open neural tube defect. As an example, the cost of preventing the birth of one open neural tube defect survivor in a population with a prevalence of 1.25/1000 could be compared with using the same financial resources to carry out 2500 cytological examinations and further treatment where necessary of 5 coronary bypass operations or 18 hip replacement operations.

Although value judgements and alleviation of human suffering defy actuarial analysis, in these days of limited resources such assessments become essential.

SCREENING POLICIES: THE PRESENT SITUATION AND BEYOND

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The only scientifically established method of screening for neural tube defects (NTDs) is maternal serum alpha-fetoprotein (MS-AFP) measurement. The detection rate and the false-positive rate resulting from different screening policies can be predicted. Optimal efficiency is achieved policies where the MS-AFP test is scheduled for 16-18 weeks' and a gestational age estimate based on biparietal diameter measurement is available to interpret the result. Variations in policy relating to repeat testing or adjusting levels to allow for maternal weight, or using separate cut-off levels for blacks, diabetics and twin pregnancies will have relatively little effect.

In 1985 an estimated 59% of all pregnant women resident in England and Wales had MS-AFP tests. There was considerable variability in the extent of screening from almost all women in some Regions (eg Oxford, Trent, NE Thames) to almost none in others (eg East Anglia). There is no evidence that considerations of NTD prevalence in the absence of screening have had a major influence on this. The use of ultrasound as an alternative method of NTD screening is likely to have contributed to the lack of MS-AFP screening in some Regions.

In the second half of 1985 among anencephalic pregnancies terminated following antenatal diagnosis in at least 64% of cases an ultrasound examination was the initial reason for suspicion of an anomaly and among spina bifia pregnancies the proportion was at least 28%. There is no scientific basis for

ultrasound NTD screening. Two studies of routine 'anomaly scanning' have been published. Their combined results show a detection rate of 100% (6/6) for anencephaly and 62% (10/16) for spina bifida. In the six published studies of selective 'anomaly scanning' done on women at high risk of NTD the combined results show detection rates of 100% (172/172) and 86% (180/209) respectively with a false-positive rate of 1.5%. If the results obtained in high risk pregnancies could be shown to be obtained when applied to the general population and at an acceptable cost then there would be a case for ultrasound replacing MS-AFP screening for NTDs. The Medical Research Council has recently agreed to support a large multicentre study to investigate this, and the related question of whether 'anomaly scanning' can replace amniocentesis. On the basis of the published results the diagnostic accuracy of selective ultrasound would appear to be much less than that for amniotic fluid AFP and acetylcholinesterase measurement. Despite this some centres will avoid amniocentesis in women with positive MS-AFP tests if a subsequent ultrasound result is normal.

Monitoring is an important feature of any screening policy. With MS-AFP screening there are standard biochemical quality assessment techniques for the assay, and epidemiological methods of ensuring an acceptable false-positive have been described. It is more difficult however to monitor the detection rate. The screening centre itself often does not have the manpower to obtain adequate follow-up of screened women and is probably too small a unit to provide a statistically reliable estimate of the detection rate. Monitoring needs to be on a national scale.

Routinely collected data on birth notifications and terminations of pregnancy are inadequate for this. For example less than one-third of the 80% fall in NTD birth prevalence between 1964-72 and 1985 can be accounted for by the published figures on terminations. Either there has been a sharp fall in incidence (coincidentally at a rate similar to the rate of increase in terminations) or there is gross underreporting of terminations following an NTD diagnosis. For monitoring to be effective antenatal diagnosis of NTDs would need to be notifiable, providing details of the method of screening and diagnosis or alternatively the reporting of termination of pregnancies following diagnosis of NTD would need to be improved, ensuring completeness and providing details of how each diagnosis was made.

Until recently the only practical way to screen for Down's syndrome was to use information on maternal age.. This has limited potential because of the low detection rate and because older women include a disproportionately large number who are likely to decline the offer of antenatal diagnosis and a therapeutic abortion either because they would prefer not to delay further the completion of their families or because they are concerned about the possibility of no longer being able to conceive. The detection rate can be increased by chosing a lower cut-off age, but this will necessarily increase the false-positive rate, possibly to an unacceptably high level. The association between low MS-AFP and fetal Down's syndrome first reported in 1984 has now been repeatedly confimed and the addition of MS-AFP screening to maternal age screening

goes some way to increasing the detection rate without incurring too high an amniocentesis rate. The combined results from 13 studies including 405 cases of Down's syndrome show that levels are reduced by about one-quarter on average. An optimal way to combine information on MS-AFP and age is to estimate each individual woman's risk of a Down's syndrome birth given her particular age and MS-AFP level. A result is screen positive if the risk is high, and a 35% detection rate can be achieved for a 5% amniocentesis rate.

Such a policy means that some women in their early 30s and late 20s will be identified, on account of having a low MS-AFP, as being at high risk of fetal Down's syndrome and therefore suitable candidates for a diagnostic amniocentesis. Similarly some older women (whose age-specific risk may be high) would be identified, on account of a high maternal serum AFP level, as being at a low risk of fetal Down's syndrome and would therefore be unsuitable candidates for amniocentesis. This form of screening has already been successfully implemented in screening programmes in the USA and in a pilot programme by NE Thames Regional Health Authority.

Other biochemical screening tests for Down's syndrome are currently being developed. Early results indicate that estimating risk by combining information on age, MS-AFP and maternal serum unconjugated oestriol could yield a detection rate of 45% for an amniocentesis rate of 5%. Using age alone 15% of women would require amniocentesis to achieve such high detection.

Another development which might affect future policy is the possibility of first trimester biochemical screening for Down's syndrome. This is also being investigated at present.

As with NTD screening local monitoring of the Down's syndrome detection rate will be difficult, and may be hindered by only about half of Down's syndrome infants being diagnosed at birth. However, collecting routine information from the relatively small number of cytogenetic laboratories in the country might provide sufficient data on which to base a monitoring programme.

WOMEN'S EXPERIENCE OF AND ATTITUDES TO SCREENING

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Many studies have been conducted on women's (or couples') attitudes towards and experience of various types of prenatal screening (in particular amniocentesis and ultrasound). In the time available it is not possible to give a thorough review of the British or international literature in the field, so I propose to highlight 6 major points.

1. Selective or mass prenatal screening programmes create a large number of sub-groups of couples differing in their experience of the programmes and in the outcomes of their pregnancy. Research on attitudes to screening has tended to ignore the complexity and variety of trajectories through the screening systems (see diagram), and the extent of variation between women or couples.

2. Prenatal screening is a form of secondary prevention but is often presented or understood as primary prevention, and may be seen as diverting effort from tertiary prevention (care of those born handicapped).

3. The difference between relative and attributable risk may not be clearly presented or understood (ie that although the risk of giving birth to a Down's syndrome baby rises after 35, most babies with Down's syndrome are born to mothers under 35).

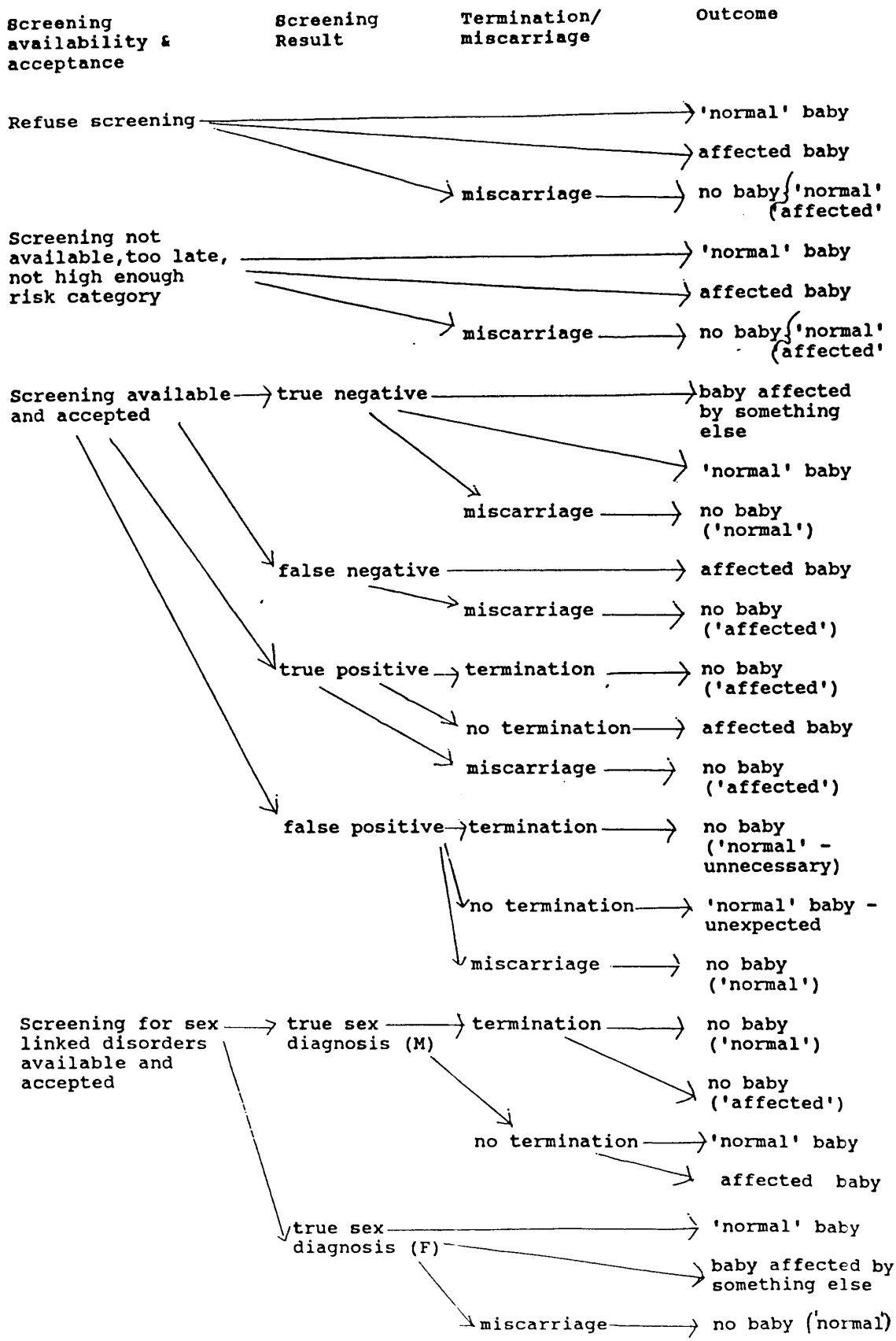
4. The setting in which screening is offered and conducted, and the manner in which results are communicated to couples, are very important. 'No news is good news' is a particularly poor strategy for conveying results, and health service personnel need to be sensitive to the anxiety created by the existence of the screening programme.

5. Most reproductive decision-making does not fit a 'rational-analytic' model, and there is no reason why decision-making in respect of pre-natal screening or its results should be any different.

6. Surveys showing general satisfaction with screening programmes are not very informative since a) most people express satisfaction with the form of health care they receive (whatever it is) and b) the more general the evaluation people are asked to make of any service the more positive their replies are likely to be.

PATHWAYS THROUGH PRENATAL SCREENING

MACINTYRE 1987



ECONOMIC EVALUATION OF SCREENING FOR FETAL AND GENETIC ABNORMALITY

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THE COST-BENEFIT APPROACH

This paper addresses the economic issues surrounding screening for fetal and genetic abnormality using the framework of cost-benefit analysis (CBA). The essence of the cost-benefit approach is that a programme 'passes the cost-benefit test' if the value of what is gained exceeds the value of what has to be given up, and 'fails the test' if the value of what is gained is less than the value of what has to be given up. Some programmes have to be forgone as a result of undertaking others because the total resources available are limited. Only by undertaking those programmes that pass the cost-benefit test will the total benefits to society be maximised. (And, obviously, only by subjecting programmes to CBA will it be known which programmes pass the test). This is the reason for undertaking economic evaluation.

Screening for fetal abnormality does, however, pose special problems. Prenatal diagnosis is usually offered with the intention that if a serious abnormality is detected then the woman may have her pregnancy terminated. Abortion is a subject about which many people have deeply held and widely differing views. For some people the idea of abortion is so abhorent that they could never contemplate it, no matter how seriously damaged the fetus might be. For them the immorality of abortion outweighs everything else. Clearly, analysis of other possible costs and benefits of prenatal diagnosis is irrelevant for them. The argument of this paper is therefore not addressed to them.

Other people, however, do wish to know whether their prospective offspring will have any serious abnormalities and, if so, would consider an abortion, which may be permitted under the existing legislation. The argument of this paper is intended to be relevant to this latter group, and to the health service decision-makers whose decisions affect their access to screening programmes. A wide range of pros and cons, including moral qualms, may be taken into account in their decisions, and analysis of these and other advantageous and adverse consequences for others should be included in CBA if it is to be useful for health service decision-makers.

CBA claims neutrality with respect to the ethical issues surrounding abortion. Rather it stresses the generality of its approach, in the full knowledge that different people attach different values to particular factors and may thus arrive at different conclusions while using a common framework.

Despite the difficulties posed by the ethical issues, a significant number of studies now exist which have estimated the resource costs, resource savings, and other consequences of a range of screening programmes. Their approach and their findings form the main subject matter of this paper.

The first stage in setting about cost-benefit analysis is to describe all the costs and benefits that need to be measured. Costs and benefits of prenatal screening are set out in Table 1. All resource consequences, and other advantages and disadvantages, should be included, whether they are goods sold by private companies, services provided 'free' by the public sector, or consequences felt only within the household. For ease of reference the costs and benefits in Table 1 are labelled as 'tangible' and 'intangible'.

Very often it is only the tangible costs and benefits that are measured in monetary terms, while the intangible factors are left as qualitative descriptions. This need not matter. If all concerned agree that the intangible benefits outweigh the intangible costs, and the analysis demonstrates that the tangible benefits are greater than the tangible costs (ie there is a 'net saving of resources'), then the programme passes the cost-benefit test.

In other cases, however, the tangible benefits may be less than the tangible costs (ie a 'net resource cost') and then the amount by which the intangible benefits outweigh the intangible costs does matter in coming to a decision about whether the intangible gain justifies the net resource cost. It should again be stressed that the role of the economist in this process is only to set out the analysis and to indicate where value judgements are needed, not to impose his or her own value judgements where measurements are missing.

ECONOMIC EVALUATIONS OF SCREENING PROGRAMMES

Prenatal diagnosis of Down's syndrome is an area where there have been several economic appraisals of the costs and benefits of different programmes. The main tangible benefits from avoiding a birth of a Down's syndrome baby are the reduced costs to the family, to the health and education services, of institutional care and of the mother's lost output at work. The main tangible costs of avoiding the birth of a Down's syndrome baby are the costs incurred through undertaking amniocentesis and termination of pregnancy. The number of amniocenteses needed to detect one affected fetus will depend on the age of the women screened, since the risk per woman rises with age. While one case may be detected by screening around 20 pregnant women aged 46, to detect one case amongst pregnant women aged it may be necessary to screen around 200 women. Thus the tangible cost per case detected will rise as younger cohorts of women are offered prenatal diagnosis, as illustrated in Fig 1. As shown in this figure there will be a 'cut off' age above which prenatal diagnosis will produce net savings - shown here by the lower shaded area - and below which prenatal diagnosis will produce net tangible costs - the upper shaded area.

At what age does this 'cut off' occur? Table 2 shows the conclusions of several cost-benefit analyses that have attempted to estimate the tangible benefits and costs of screening women of different ages. From these studies it is tempting to conclude that the best estimate of the 'cut off' age is somewhere around 36, at which age the risk of having a Down's syndrome baby is around 1 in 200 (1).

While Fig 1 suggests that above the age of around 36 prenatal diagnosis 'pays for itself' and at younger ages it incurs a net tangible cost, it should not necessarily be concluded that screening younger women would diminish the overall benefits, since the intangible benefits and intangible costs have not yet been incorporated into the analysis. The intangible benefits include the reassurance to the majority of prospective parents that their baby is (probably) not going to be handicapped, or for the minority where Down's syndrome is detected, being able to choose whether to terminate the pregnancy and try again to conceive a non-handicapped child. The intangible costs include aroused anxiety, the discomfort, inconvenience and possible complications of amniocentesis and the possibility of losing a non-handicapped fetus as a result of amniocentesis. It could plausibly be argued that the intangible costs and benefits will be proportional to the tangible costs and benefits. For example, the risk of fetal loss owing to amniocentesis was

estimated at about 1% by the UK 'MRC Working Party on Amniocentesis' (10) although it is now claimed that the risk, in experienced hands, is only about 0.5%. If prospective parents feel that the risk of losing a non-handicapped fetus of 0.5% balances the risk of having a Down's baby of 0.5% then assessment of the intangible costs and benefits may also suggest a cut-off age of 36 - where the risk of Down's syndrome is 1 in 200. Clearly this discussion of the relative magnitudes of the intangible factors is speculative, however, and requires further research.

Another way of identifying women who may be at high risk of having a Down's baby could be from analysis of maternal serum alphafetoprotein (AFP) levels. If this is feasible then offering prenatal diagnosis to such women should produce the same sort of net resource savings as with women screened on account of age-related risk. Gill, Murday and Slack (11) have estimated that the net resource savings could be very substantial.

Of course the major use of AFP screening is to detect the main open neural tube defects - spina bifida and anencephaly. The tangible cost of avoi ding the birth of one infant affected by open neural tube defect was estimated by Hibbard et al (12) to range from around £7200 to £8700, if the incidence were 1.25 per 1000. Table 3 shows the health service costs and effects of the most expensive of the options described by Hibbard et al - a programme of routine ultrasound scanning and serum AFP measurement for all women, followed by diagnostic ultrasound and amniocentesis for women with a serum AFP level above the 97th centile. They estimated that this would cost £735,600 (1980 prices) per 100,000 women, and would lead to the avoidance of the birth of 340 infants affected by open neural tube defects - a cost per birth avoided of £2164. If, however, open neural tube defects were 4 times rarer than for the population they studied in South Wales - 1.25 /1000 instead of 5/1000 - then the cost per birth avoided would be 4 times higher - nearly £8700. This figure represents a more reasonable average for spina bifida births in Great Britain as a whole, where the 'natural' birth prevalence rate is probably around 1.25/1000 (14).

The saving per spina bifida birth avoided has been calculated to be between £16,200 and £21,600 (1979/80 prices) - see Table 3. Comparing the cost with the saving suggests that AFP plus ultrasound screening programmes (as described by Hibbard et al.) produce net resource savings where the 'natural' birth prevalence rate of spina bifida exceeds 1.25/1000.

Neonatal screening for conditions such as phenylketonuria can allow affected children to be treated, leading to the prevention of handicap. Bush, Chen and Patrick (15) examined the tangible costs and savings to the health sector in New York State of a programme to diagnose phenylketonuria (PKU) in neonates. The saving of expenditure on institutional care of the handicapped alone was estimated to exceed the cost of the screening programme, producing a net saving of $12000 per case (1970 prices). Other tangible benefits such as the extra output produced at work would have added to the net saving.

Komrower et al, (16) calculated the costs and cost-savings attributable to the Manchester PKU screening programme in England. They too found a net health service resource saving. (although their economic methodology could be criticized in particular for the failure to discount future costs, recalculating their figures using a 5% discount rate would not reverse their overall conclusion of a net saving).

MEASURING INTANGIBLE BENEFITS

The study by Bush, Chen and Patrick (15), as well as measuring the health sector resource consequences, attempted to quantify the improved health of those who would be treated for PKU. They asked medical consultants to predict the levels of disability with and without treatment of PKU. The consultants were then asked to rate the desirability of these disability levels on a scale from 0 - equivalent to death, to 1 - equivalent to complete health. The results, over the life cycle, for classic PKU are shown in Fig 2. The upper line - treated cases - shows the dys-function imposed by the special diet during early childhood, but then follows a normal form representing the general mortality rate. The lower line - untreated cases - shows the lower levels of function and higher mortality rate of those severely retarded by PKU. The difference between the two lines is a measure of the improvement in health attributable to the screening programme, in this case 47 'function-years', or 'quality-adjusted life-years' as they are now more commonly termed.

It should be possible, at least in principle, to extend this type of measurement to other programmes aimed at reducing distress and handicap. But why should we want to? The reason relates to my initial assumption - that one objective of the health service would be to try to secure the maximum benefits with the resources available. Some of the benefits of screening programmes in this area are the increased capabilities - or improved health, broadly defined - of those people for whom handicap is prevented. Being able to compare programmes in terms not only of their net resource costs but also their health benefits can assist the formulation of priorities for resource allocation, so that total benefits are maximised.

EXTENSIONS

The studies discussed here indicate that in the UK prenatal diagnosis for open neural tube defects and for Down's syndrome where the risk is greater than 1 in 200, and neonatal screening for PKU all produce net savings of resources - or 'pay for themselves'. However, it does not necessarily follow that extending such programmes would produce further resource savings. Indeed one implication of Fig 1 is that extending amniocentesis to women under 35 years old (in the absence of other risk indicators) would probably incur net resource costs. This is also likely to be true of extensions to other screening programmes. Attempts to increase attendance for prenatal AFP screening will incur resource costs for extra publicity and so forth, making the screening of the extra women more expensive than the average. Thus rising net resource costs for extensions to screening programmes are likely to be the rule rather than the exception.

Whether or not the resources available for screening programmes are increased, it would therefore seem important to set priorities by examining the additional costs and additional benefits of further programmes. In doing so it would be wise to measure directly the extra costs, and benefits, of programme extensions rather than making projections from the average costs, and benefits, of existing programmes, to try to measure any resulting health improvements in terms such as quality-adjusted life-years gained that can be compared with the benefits of other programmes, and to try to make assessments of the intangible costs and intangible benefits to parents especially. Hence there is likely to be a key role, in providing relevant information, for further economic evaluations of the kind discussed here.

Table 1 Classification of Costs and Benefits of Prenatal Screening

	COSTS	BENEFITS
TANGIBLE	1.1 organisation of primary health care services to identify women at high risk and inform them about prenatal diagnosis at an early stage of pregnancy. 1.2 health service costs of diagnostic procedure 1.3 laboratory analysis of sample 1.4 woman's diagnosis attendance travel costs and opportunity cost of time 1.5 possible repeated costs of 1.2 - 1.4 1.6 health service costs of terminating pregnancy 1.7 woman's abortion attendance travel costs and opportunity cost of time 1.8 cost of counselling 1.9 loss of child's possible future productive output	positive test result and termination of pregnancy leading to: 2.1 avoided health services expenditure 2.2 avoided education services expenditure 2.3 avoided other public services expenditure 2.4 avoided lost maternal output through rearing child 2.5 avoided family expenditure on child 2.6 avoided child's lifetime consumption of other goods and services
INTANGIBLE	3.1 anxiety aroused through being informed of high risk 3.2 qualms about contemplating abortion 3.3 discomfort of diagnostic procedure 3.4 anxiety before test result received 3.5 distress after miscarriage thought to be caused by diagnostic procedure 3.6 possible fetal damage caused by diagnostic procedure 3.7 abortion of non-handicapped fetus owing to false positive test result 3.8 possible complications for woman 3.9 false reassurance and possible harm to relationship with child owing to false negative test result.	4.1 avoided distress to parents (and others) of having handicapped child owing to positive test result and termination of pregnancy 4.2 reassurance to parents owing to true negative test result 4.3 greater likelihood of trying again to conceive a non-handicapped child

Table 2.

Tangible benefits and costs of prenatal diagnosis of Down's syndrome

Maternal age over which prenatal diagnosis has been estimated to produce a net saving of resources

Study	Country	Maternal age
Conley and Milunksy (2)	USA	35
Glass (3)	UK	40
Hagard and Carter (4)	West Scotland	35
Mikkelsen et al. (5)	Denmark	35
Passarge (6)	West Germany	36
Sadovnick and Baird (7)	Canada	34
Andreano and McCollum (8)	USA	36
Gardent et al. (9)	France	38

Note: These studies do not use identical assumptions, methods, discount rates etc. For details see original sources.

Table 3.

Screening for open neural tube defects in the UK

Programme of routine ultrasound, serum measurement; diagnostic ultrasound and amniocentesis for women with serum AFP above 97th centile (Hibbard et al. (12)).	
Cost per 100,000 women (1980 prices)	£735,600
Births avoided, per 100,000 women where 1 in 200 affected	340
Cost per birth avoided:	
where 1 in 200 affected	£2,164
where 1 in 400 affected	£4,328
where 1 in 800 affected	£8,656
Saving per spina bifida birth avoided (1979/80 prices; Henderson (13))	
Discount rate 3%	£21,600
5%	£18,500
7%	£16,200

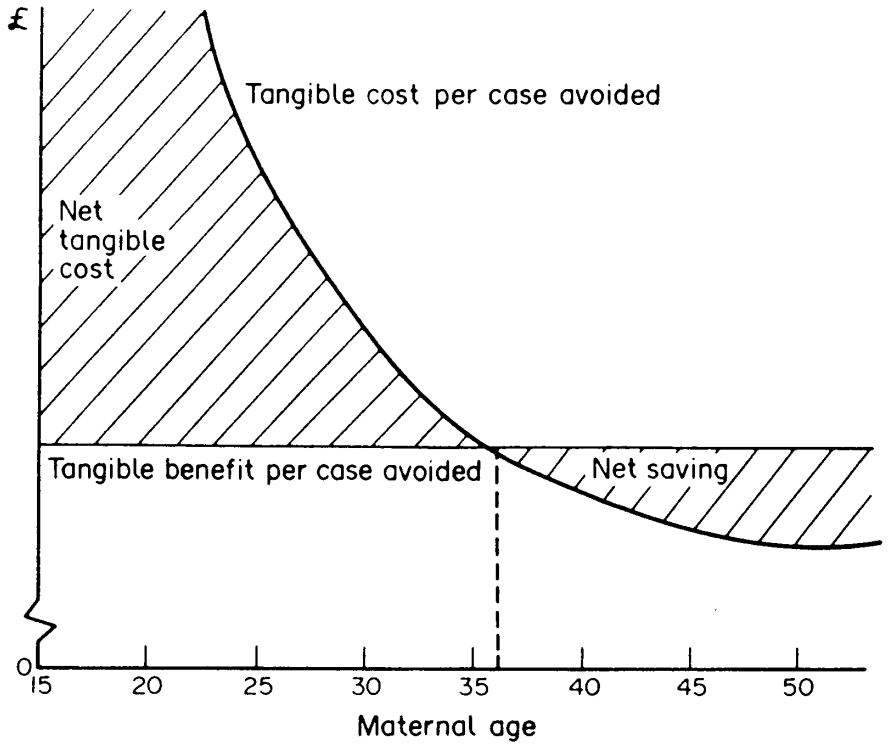


Figure 1. Tangible benefits and costs of prenatal diagnosis of Down's syndrome.

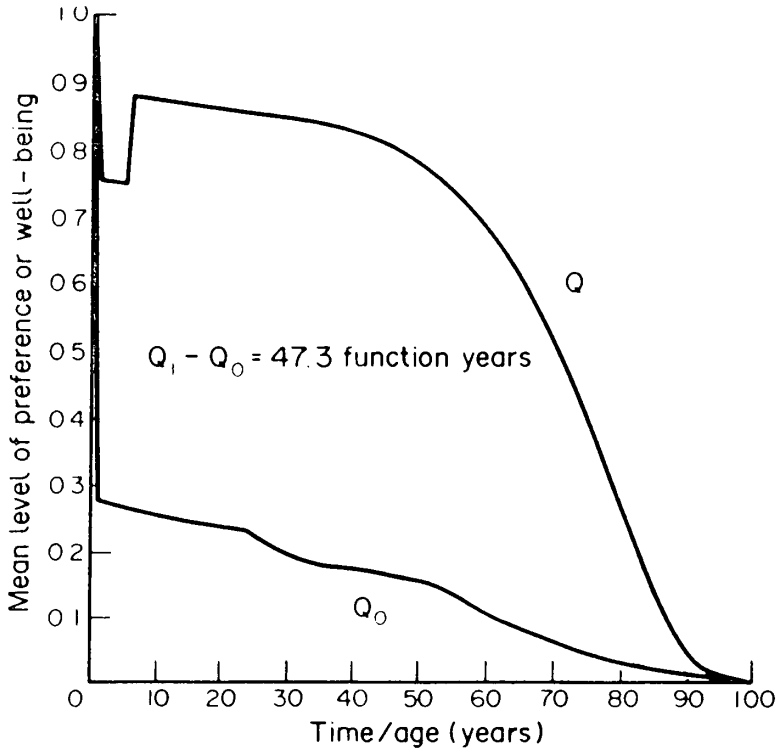
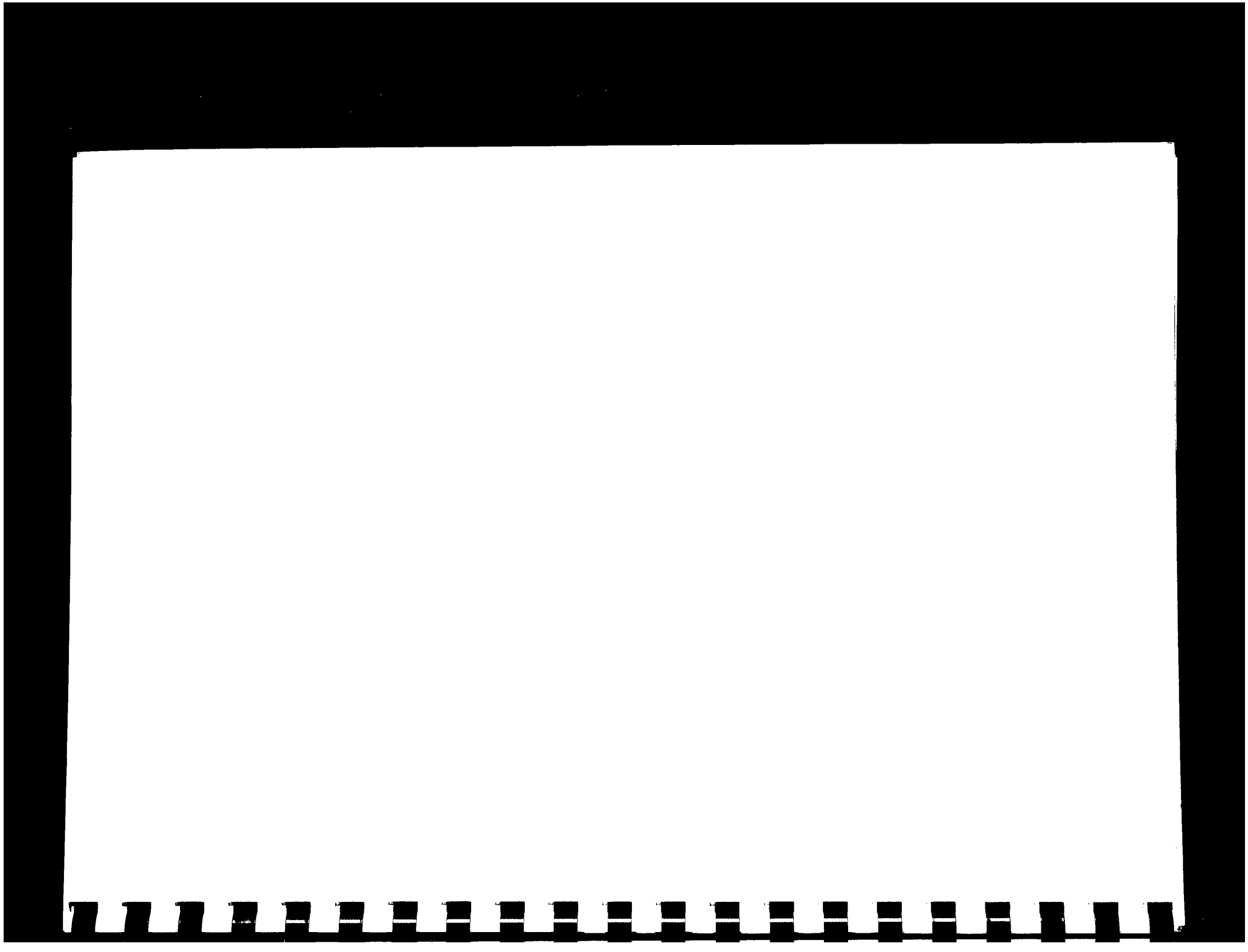


Figure 2. Mean level of well-being over time for classic PKU with and without treatment using consultants' value set. Upper line, representing treated cases, depicts initial dysfunction imposed by diet during first 6 years, then gradual decrease in mean function imposed by general mortality rate. Lower line (untreated cases) shows lower levels of function and also higher mortality rates experienced by severely retarded.



SCREENING FOR INHERITED DISEASE
- CYSTIC FIBROSIS -

Professor D J H Brock
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Cystic fibrosis (CF) is one of the most common recessively-inherited genetic disorders found in populations of North-European ancestry. Newborn screening programmes show a birth incidence in the United Kingdom of about 1 in 2200, corresponding to a heterozygote frequency of 4.7%. The BPA survey estimates the UK population prevalence to be 1 in 12155, and the total number of CF homozygotes to be 4693. Prognosis has shown improvement in the last 30 years, with median survival for males at 23.5 years and for females at 19.5 years
The UK prevalence appears to be increasing at about 100 cases a year (Professor J Dodge, personal communication).

CF is an expensive disorder to manage. Lamb and David made a comparison of the inpatient costs of the major health care groups seen at Booth Hall Children's Hospital and showed CF at £1606 per admission to be the most expensive. They estimated 1.23 admissions per patient per year, which with a 20-year average life-span, gives a life-time inpatient cost of £39,000 per patient. The total annual inpatient costs for 4693 CF patients are estimated at £9.3 million. However, these crude figures take no account of outpatient costs, of state benefits or of the loss of productivity in a group of patients with a drastically reduced life-span.

Prenatal diagnosis of CF is now available to couples with a high risk of bearing an affected child. The method of choice

uses first-trimester chorionic villus sampling and a panel of linked DNA markers to track the mutant gene.
Virtually all couples are fully informative if enough markers are used, although the probe p79a has an unacceptably high recombination rate with the CF gene. In most cases it is necessary to genotype an index affected child to establish the phase relationships between markers and the CF gene (Figure 1). If no index affected child is available, or if the family is only partially informative for DNA markers, prenatal diagnosis can be carried out by measurement of microvillar enzymes, on second-trimester amniotic fluid supernatant. This method is cheap and rapid, but is associated with a false negative rate of about 5% and a false positive rate which may be as high as 8%
Microvillar enzyme testing can also be used to exclude CF in pregnancies where prior odds are less than 1 in 4, but is not effective in detecting affected fetuses.

If all couples with an affected child accepted prenatal diagnosis in subsequent pregnancies, it would have a comparatively modest impact on the birth prevalence of the disorder. In England and Wales in 1985, 32.3% of live births were to married women who had not had a previous child, while 19.2% were illegitimate births. Thus in only about 50% of pregnancies would prenatal diagnosis be feasible and in only one quarter of these would a CF fetus be detected. Furthermore, the mean age of diagnosis of CF in the UK is 1.82 years, so some couples would embark on second high-risk pregnancies without the knowledge that they were heterozygotes. For this reason prenatal diagnosis, per se, would be unlikely to reduce the birth

prevalence of CF by more than 10%. The only realistic approach to a major reduction in the 300 annual UK births of CF is through a policy of prenatal screening (Figure 2).

Although the technology for prenatal screening for CF is not yet available, there are signs that it is imminent. The most important of these is the indication from linkage disequilibrium data that CF is the consequence of a very limited number of mutant alleles at a single genetic locus (perhaps analogous to sickle cell anaemia). Thus even if the product of the mutant gene is an internally-localised membrane protein (R Frizzell, personal communication), expressed in a limited range of inaccessible tissues (e.g. sweat glands, pancreas, lung), direct DNA analysis should be possible on any nucleated tissue (white blood cells, chorionic villi, etc). This could be achieved on Southern blots with hybridisation to appropriately tagged oligonucloetides. Even more promising is the prospect of using the polymerase chain reaction to amplify the relevant portion of genomic DNA to a point where single or double doses of the mutant gene can be visualised on acrylamide gels with or without prior hybridisation, or on dot blots by hybridisation to specific oligonucleotides.

Prenatal screening for genetic disorders has been used successfully for Tay-Sachs disease and for β-thalassaemia in defined ethnic subgroups. It has not hitherto been attempted for a genetic disease distributed evenly through most of a national population. The numbers are formidable, though less so when compared to those dealt with in maternal serum AFP screening for neural tube defects. There are currently no

methods suitable for mass testing for CF heterozygosity, and therefore it is not possible to calculate the costs of prenatal screening or the benefit-cost ratio of reducing the incidence of the disorder. But it is probable that improvements in DNA technology (e.g. the polymerase chain reaction) will soon make it less expensive and more suitable for handling large numbers of samples. Commercial laboratories are aware of this possibility and may precipitate screening programmes by making the appropriate reagents available in kit form. Although at first sight this might seem to be the opening of a Pandora's box, inspection of other autosomal recessively-inherited diseases segregating in the UK population suggests that CF is a somewhat special case.

IMPACT ON THE FAMILY

Mrs Christine Lavery
Honorary Secretary
The Society for Mucopolysaccharide Diseases

1. A handicapped child in the family

Like a majority of first time mothers I was oblivious to the statistic that approximately 1 in 50 babies born in the United Kingdom will suffer a major handicap and that around 25 babies born each year will be suffering from a Mucopolysaccharide Disease. Neither was I aware that I carry the X-linked condition Hunter Disease.

Very rarely is this condition recognised at birth although it is present from the moment of conception. My husband and I were grateful that Simon's diagnosis did not follow for 20 months and we had time with our child in blissful ignorance of what lay ahead. The 'getting to know your baby process' is very imporant and the relationship is not easily broken once established.

We, like most families of a severely handicapped child, could not turn our backs on Simon and it is true to say that his endearing character brought out the best in our family. Simon is one issue, deciding to bring another affected child into the family is quite different.

Learning that your child has a severe handicap affects individuals differently. Some families will cope admirably with a child suffering from spina bifida, Downs or an MPS Disease whilst other families would find a much lesser handicap in their child intolerable to cope with.

2. Genetic counselling

Having learnt that they are at risk of producing a handiicapped baby, many parents need to give themselves time to think and see the light again. Some may decide to abandon any thoughts of enlarging their family, others have a desperate desire to bear a healthy child. It is important that genetic counselling is handled confidently and sensitively. Some families have left a genetic counsellor's office more confused than when they entered. Considering there are many rare conditions perhaps the answer is to set up specialist genetic counselling facilities at regional centres.

3. Considering further pregnancies

I can speak from experience on prenatal diagnosis but have no personal experience of termination. So I distributed 175 questionnaires inviting families to give personal experience of prenatal diagnosis and/or termination of pregnancy for fetal abnormality. I invited information on how the diagnosis was presented, nursing attitudes during hospital stay and degree of help forthcoming from the primary health care team. Over 100 questionnaires were returned taking in prenatal diagnosis and termination for anencephaly, missing abdominal organs, congenital heart disease, Down's syndrome, hydrocephalus, Patau's syndrome, Potter's syndrome, spina bifida, trisomy 7, 9, 13 and 18, a translocation, Turner's syndrome and several types of MPS disease.

Many families at risk seek genetic counselling before deciding on a further pregnancy. They will consider how they will cope with an affected child but faced with the actuality, couples need to go through the realisation and decision making process - basically the human race are optimists and such things don't really happen to my or your husband or wife.

For some families termination is unacceptable but this should not prevent a family seeking prenatal diagnosis. Families felt that it would have helped considerably if they could have known the status of the baby even though they would be unlikely to terminate.

4. Prenatal diagnosis

It is different for families where the first indication that anything is amiss comes during an ante-natal visit, a scan or following chorion biopsy or amniocentesis for maternal age. Most such couples who responded were not anticipating a problem and had not addressed such a possibility. With few exceptions, where the abnomality was found during examination or scan the diagnosis was presented sensitively and questions answered honestly. However, many felt that the sequence of events followed too quickly for the couple to feel in control and there is a need for all hospitals to allow participation by the father at ante natal level including being present during a scanning and prenatal diagnosis.

A large majority of couples learn the results of their amniocentesis or chorion biopsy over the telephone from the hospital. Although always dealt with sensitively, is it not possible for the news to be broken by the primary health care Team or family GP? Often mum was alone at the time the news was broken and faced the added burden of giving bad news to her partner. In my sample of 70 mums who have undergone at least one termination, hindsight suggests that details on groups of parents offering support (e.g. SAFTA) would have helped enormously and give the oportunity to share experiences with someone who had been in a similar situation, helping to ease the emotional pain and guilt of terminating a much wanted baby. In almost all cases parents were ignorant of what an induced labour involved and were resentful that husbands in many cases were not welcome.

5. Terminating a much wanted pregnancy

If only it could be routine for the consultant to take time to discuss the termination procedures before they happen, to introduce the midwife who will be with the couple during delivery, to talk about what will happen to the baby. Some mums felt that holding the baby made it real but in shock many declined the opportunity, in the weeks, months, even longer after termination the regrets crept in. I believe hospitals should routinely provide a photo of the baby and tell couples that although in law a baby born dead before 28 weeks gestation does not require a funeral, there is no reason why he or she should not be buried. The important point is that however distressing, for both the couple and the medical team all this information should be given. It is not for the medical or nursing team to decide for them.

6. Follow-up care by the Primary Health Care Team

In most cases follow-up by the primary health care team was virtually non-existant for a mum returning home following an induced labour termination. Many mums were in need of some professional support but felt let down as their GPs did not visit them and a visit from the health visitor was too late. The primary health care team must acknowledge that these mums need to talk, to go through the physical experience, the fetus is a baby to these mums however many weeks gestation. Don't worry about upsetting mum, she is already upset and avoiding the subject is likely to upset her even more. The overwhelming message from the mums who completed the questionnaire is 'please establish a standard of follow-up care on the same lines as that afforded to mums who bring home their baby'.

Afterall, we have just given birth to much wanted babies but our arms and hearts are empty.

THE HAEMOGLOBINOPATHIES

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Single-gene disorders are transmitted in a Mendelian fashion, with dominant, sex linked or recessive inheritance. Genes for dominant and X-linked disorders are relatively few in number, so that even if accurate methods for carrier-detection existed, population-screening would be too inefficient to be feasible. However, since these genes have a high potential for causing trouble to their carriers, many may be identified through a family history.

The number of genes for disorders with dominant inheritance such as Huntington's chorea or achondroplasia, eventually approximately equal the number of people with the disease. Therefore there is practically always a family history, unless the disease is due to a new mutation. (Conditions with a very negative effect on reproductive ability, such as major congenital heart disease or achondroplasia are often due to new mutations).

Examples of sex-linked disorders are Fragile-X linked mental retardation, which may affect 1/100 boys, haemophilia, Duchenne Muscular Dystrophy and Lesch-Nyhan syndrome. About one third of the genes for X-linked disorders are carried by affected males, and about two-thirds by healthy female carriers, who have a high reproductive risk, regardless of their choice of marriage partner. Since these conditions can be passed on for several generations through unaffected female carriers, a family history is not as common as for dominant conditions. The frequency of lethal X-linked conditions is maintained by a high mutuation rate. For instance, about one third of cases of Duchenne Muscular Dystrophy are due to new mutations, and so could not be signalled by a family history.

The vast majority of abnormal genes are recessive, i.e. are only a potential problem until a carrier mates with another carrier of the same pathological gene, so these diseases usually occur in an apparently sporadic way, most affected infants being born to couples of carriers with no prior family history of the disorder. Most people carry one or more potentially lethal recessive genes and even a rare recessively-inherited disorder may indicate a relatively large number of carriers.

The offer of prenatal diagnosis for inherited diseases depend on the ability to identify carriers, or people with a high probability of being carriers. For dominant and X-linked conditions this may be done through the family history, and in principle (when cheap and simple carrier testing and prenatal diagnosis are possible and available, and if take-up rates by potential carriers are high) a high proportion of cases could be detected prenatally and the birth-rate of individuals with disorders like Huntington's chorea could be greatly reduced. However, only about two thirds of cases of muscular dystrophy could be prevented, because of the high spontaneous mutation rate.

By contrast, for recessively-inherited diseases, carriers must be identified through population screening. In recessively inherited conditions, couples at risk have a 1 in 4 chance of having an affected child in each pregnancy. In most cases heterozygotes still cannot be

detected with any degree of accuracy, so counselling and prenatal diagnosis can be offered only after the birth of the first affected child has proved that both parents are carriers. Under these circumstances, if every couple ultimately had 4 children, prenatal diagnosis could be provided in 38% of all pregnancies. But in most of Europe final family size is limited to 2 or 3 chldren, so in practice prenatal testing can be offered in only about 12% of pregnancies at risk, and, though an invaluable service for couples with an affected child, has a near-negligible effect on the total number of affected children born. By contrast, with the haemoglobinopathies (the thalassaemias and sickle-cell disease) all at-risk couples can be detected prior to reproduction by cheap and simple blood tests, and prenatal diagnosis is possible in both the second and the first trimester of pregnancy.

When prospective heterozygote diagnosis for a common and serious recessively-inherited disease such as cystic fibrosis becomes possible, the implication that everyone will need to be offered testing at some stage is sometimes found alarming. However, the implications can be fully explored by reference to the thalassaemia control programmes of southern europe, which answer many questions about the social implications of heterozygote screening.

Patients with B-thalassaemia major are healthy at birth, but develop a severe intractable anaemia between 6 months and 2 years of age. In the absence of diagnosis and treatment, most die from anaemia or infection before 5 years of age. Patients with sickle cell disease suffer from anaemia, and sickling of deoxygenated red blood cells in various organs leads to unpredictable patterns of morbidity and mortality. The risk to life is greatest in early childhood, when trapping of sickled red cells in the spleen can lead either to sudden profound anaemia and death from an acute 'splenic sequestration crisis', or to functional asplenia and sudden death from overwhelming infection. Most survivors of the hazards of childhood have life-long clinical manifestations of chronic anaemia, and recurrent episodes of pain and other complications often requiring hospital admission.

Management of both sickle cell disease and thalassaemia major is burdensome, expensive and life-long. However, it is cheap and easy to detect the symptomless carriers. When couples of carriers are informed of their genetic risk and offered prenatal diagnosis most couples at risk for thalassaemia and some at risk for sickle cell disease use prenatal testing and selective abortion of affected pregnancies in order to ensure a healthy family: so many births of affected children can be prevented when screening and counselling is provided.

When the existing mediterranean programmes were started in the 1970s, the concept of prevention of a common inherited disease at the community level was fairly new, but they now provide a model for developing such services. They have shown that prospective carrier testing and counselling requires an organised programme for informing the population of the reality of a genetic risk. It is necessary for people to realise that they themselves might be involved, and to explain the mode of inheritance, that healthy carriers can be identified, and that serious consequences can be avoided.

The educational programmes must motivate people to seek testing at an appropriate time, and there should be easy open access to reliable testing. Finally, and most important, appropriate resources for genetic counselling, both written and verbal, must be freely available, to ensure that the facts are really understood.

The programmes are monitored by following the fall in the birth-rate of affected children after the start of a programme. The results show that new births of affected children have almost ceased in some areas, and that most residual births were due to ignorance of risk, rather than to rejection of prenatal diagnosis. In this case, incomplete prevention is a measure of incomplete information and education of both the medical service and the community.

The most important problem facing couples at risk for infants with severe inherited disorders, is the high recurrence risk. When prospective heterozygote diagnosis is available most couples at risk become aware of their problem prior to reproduction, and many go through the trauma of prenatal diagnosis repeatedly before obtaining the family they want. Though some achieve several healthy children without complications, others may undertake 4 or 5 pregnancies, and may still achieve only one, or no, healthy child. Prenatal diagnosis in every pregnancy is particularly stressful for the 10% of couples who are subfertile, and for women at risk for X-linked disease where it is not possible to distinguish a normal from an affected male, so there is a 50% risk of elective abortion in each pregnancy.

Though first-trimester diagnosis by CVS and gene-mapping is a major advance for couples at high genetic risk since it relieves anxiety earlier when the fetus is unaffected, and allows less traumatic termination of pregnancy when it is, the statistical problem remains unchanged. At-risk couples will remain the victims of chance until it is possible to select the genotype of the zygote prior to implantation through pre-implantation genetic diagnosis.

COUNSELLING

Ms Elizabeth Anionwu
Head of Brent Sickle Cell
and Haemoglobinopathy Centre

In 1986 it was estimated that 'there is an indication for prenatal diagnosis in up to 10 per cent of pregnancies including those in older mothers, those with abnormal serum alph-protein (AFP) levels or those with a history of genetic disorder. The advent of new techniques for looking at abnormal genes using DNA technology will increase this percentage'. (1)

The dilemmas faced by would-be parents are immense and it would appear to be a commonsense proposal that adequate counselling services are available to match the growth in high-technology genetics.

Satcher (2) has provided a pertinent definition of counselling when, in training genetic counsellors, he describes it as 'personal, private and confidential, that it should be informative and should correct misinformation, and should help people to find the care they need. It should tell what care and related options are available. It should be uninfluenced by personal opinion.
One worthwhile goal is to minimize personal opinions, judgements and directions in counselling. Counselling should lead individuals and couples to make decisions with which they are prepared to live-which means that they should know all the possible outcomes of making those decisions.'

In determining the adequacies of present counselling services for prenatal diagnosis in Britain the experience of antenatal counselling in Brent in relation to haemoglobinopathies will be used (3). Between March 1982 and October 1987 we have counselled 94 couples mainly at risk of producing a child with a sickle cell disorder or thalassaemia major-see Table 1. Most were identified through the antenatal screening programme at the Central Middlesex Hospital and other couples were referred from different parts of the Region or via the voluntary organisations.

The clinical variability of sickle cell disorders in contrast perhaps, to thalassaemia major presents one of the most difficult dilemmas for the couple and the counsellor in discussing the relevance of prenatal diagnosis. This is highlighted in the following data from the Brent Sickle/Thalassaemia register. The positive side is seen in Table 2 which gives the age distribution of 285 patients, dispelling the myth that such individuals die before the age of 21 years. The milder nature of SC disease is also demonstrated. On the negative side the clinical course is severe in about one third of patients with sickle cell anaemia and there is a 7% incidence of stroke in children (4). Finally Table 3 gives details of 13 deaths that have occured in the last 13 years.

These differences in clinical expression and the moral dilemma

of deciding which 'disability' should be prevented through termination of pregnancy is relevant for all couples asked to contemplate prenatal diagnosis. Weatherall (5) comments 'This philosophy of perfection opens up all sorts of dangerous avenues and we are going to have to be extremely careful about the choice and education of genetic counsellors in the future.'
Our policy in Brent is to discuss it with all couples but in detail with those at risk of producing a baby with sickle cell anaemia and thalassaemia major. In addition information is given about testing babies from birth for these conditions.

Counselling technique
Counselling is undertaken by haemoglobinopathy counsellors, qualified health visitors who have also undertaken an intensive specialist course. Couples can be seen in the antenatal clinic, the Brent Centre or in their home. Literature is provided on the appropriate condition including one on prenatal diagnosis;the latter on Thalassaemia has been translated into 5 Asian languages. The counselling sessions include a discussion on previous knowledge about the condition, impact of the results, nature of their respective traits, the genetic implications of recessive inheritance, the characteristics of the homozygous condition in the child and the availability of help.

In the case of sickle cell disorders the clinical variability of the condition is emphasized. As much factual information as possible is offered to enable the couple to make an informed decision. The methods and risks, as known, of the various types of prenatal diagnosis and the possible termination of pregnancy are discussed in detail. A non-directive approach is used and couples are encouraged to discuss the emotional impact of the information provided and to repeat what they have understood the counsellor has communicated. The couples are offered additional counselling sessions as well as an opportunity to talk to doctors, staff at prenatal diagnostic units, and, through the voluntary organisations, families with affected members and couples who have experienced prenatal diagnosis. Table 4 gives details of the response of 48 couples in 59 pregnancies.

Many factors appear to influence attitudes towards prenatal diagnosis, some of which are grouped as follows:-
Personal
Religion, culture & health beliefs.
Level of awareness
Prior knowledge of risk, previous information and/or experience of, and severity of condition.
Pregnancy & reproductive history
Stage of pregnancy, history of infertility and/or obstetric complications.
Age of couple, desired number of children.
Number, sex and state of health of previous children.
Prenatal diagnosis
Type available, degree of accuracy & risk of miscarriage & other complications.

Previous experience of tests and of termination of pregnancy, for whatever reason.
The experiences of the couples we have counselled have sometimes been extremely traumatic and the following reveal the gaps in present provisions:-

Not being informed of risk from previous screening.
Delay in receiving first hospital antenatal appoinment.
Delays in communicating results to couple.
Lack of sensitivity to cultural, ethnic & religious beliefs.
Failure to screen sperm donors.
The abrupt & anxiety provoking manner of communicating result, whether in the clinic, over the phone or by letter.
No counselling provided.
Too little time provided for counselling.
No counselling in appropriate language.
Directive approach.
Inadequate information.
Incorrect information.
Biased gloom-laden approach.
Prenatal diagnosis offered only if couples promise to terminate affected pregnancy.
Insufficient time to make decision.
No referral to specialist genetic counselling service and appropriate voluntary groups.
Delay in, and unsatisfactory method of communicating result of prenatal diagnosis.
No post termination counselling or referral to specialist support group e.g. SATFA (Support After Termination For Abnormality).
Counselled too late in pregnancy.
No follow up of baby.

Discussion
These experiences reveal a disturbing disparity between the advances in both the techniques and application of prenatal diagnosis and the woefully inadequate counselling facilities for those being offered the tests. The following four questions need to be urgently addressed:-

1. Who decides which conditions are 'suitable' for prenatal diagnosis, which method is the safest and most accurate and how late in pregnancy is it ethically, medically and psychologically sound to undertake the test and possible termination of the pregnancy?

2. Whose responsibility is it to ensure that the couple receive specialist counselling before, during and after the pregnancy, whatever the outcome?

3. Who should counsel, what type of training is required and who should validate, monitor and evaluate such training?

4. How can the existence of counselling services be better publicised, e.g. to general practitioners, obstetricians, midwives, health visitors and the public?

Conclusion

The inadequate nature of present counselling facilities for prenatal diagnosis is a disturbing state of affairs. There is a vital need for a network of trained counsellors, perhaps co-ordinated by Regional Clinical Genetic Centres.

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THE CONSUMER'S VIEW THE HAEMOGLOBINOPATHIES: THE ETHICAL, POLITICAL AND ECONOMIC ISSUES

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I have been asked to put the patient's viewpoint on the haemoglobinopathies which involve both sickle cell disease and thalassaemia.

The differences here are that thalassaemia is more prevalent among Mediterranean people and not so frequent among Afro-Caribbean people. Both conditions differ in prognosis because whereas with thalassaemia the course of the disease is known in that once diagnosed the patients are on regular blood transfusion regimes with desferrioxamine injections to cut down on the iron content, which is expensive and costs about £14,000 per patient per year. This helps to improve the quality of a life span of 20-30 years of age.

With sickle cell disease, which is found mainly in Afro-Caribbean people, the condition is variable with the majority of people leading reasonably normal lives with little or no treatment and the few who are badly affected only having palliative treatment with antibiotics analgesics and occasional blood transfusions.

The Ethical View

The ethical aspect of screening for haemoglobinopathies means looking at the moral issues involved. These are as follows:

1. Are we going to offer a screening service which says that couples tested, and both carrying the trait, would be offered pre-natal diagnosis and selective abortion as an alternative to having a child with the disease?

2. Are we going to offer screening with pre-natal diagnosis for a family who already has a child with the disease and has asked for screening in the hope that if the fetus is affected the couple would opt for prenatal diagnosis and selective abortion?

3. Would screening be a way of eradicating the disease?

When considering prenatal screening one has to take into consideration people's racial, cultural, educational and religious backgrounds. For example, Catholics or some African cultures may not want to abort under any circumstances.

People who are well educated in genetics may prefer not to have a child with sickle cell disease but again it must be their choice.

The eugenics side should also be considered. For example, are we going to selectively abort all the black babies with sickle cell disease when it is known that some people with the disease lead full and active lives?

The answer to the above questions lies in the education of the concerned community from senior school level and should be incorporated into the curriculum in biology and education for living classes so that by the time they reach the ante-natal clinic they are not faced with decisions that are traumatic and which involve mostly disbelief and stigma.

Because education in genetics is a new field, it should be included in medical education for all doctors and health professionals because if they do not have the facts and the knowledge they cannot pass it on to their clients.

When talking about culture and background, if parents are concerned and knowledgeable about the conditions before starting a family, when they get to the pre-screening process they will already have the knowledge to make informed decisions.

The Racial View

In this country people of Mediterranean descent who know and understand about thalassaemia as a genetic disease are prepared to accept screening, pre-natal diagnosis and selective abortion in an effort to eradicate the condition. They are a closed community in the sense that they inter-marry among their own and therefore this knowledge is passed on from generation to generation.

On the other hand, in people of Afro-Caribbean descent in this country sickle cell disease is not well known, arranged marriages are unknown and the knowledge of genetics and how this disease affects the black community is not passed on through the generations. There is therefore, not the same importance for the family and offspring.

An undercurrent of half truths exists among the black community. Sickle cell anaemia is thought of as a 'black disease' and families known to have it are sometimes avoided and ostracised. It has been confused with syphilis and lately with AIDS due to the media hype of this disease originating in Africa. As a result of continuing urging for tests for sickle cell trait and unsufficient general public information and knowledge of genetics, some adverse side effects have occurred. Individuals have been taunted, groups are being discriminated against and emotional racial overtones are obscuring realities. In some areas even the trade unions have become involved. Sickle cell disease has been termed the first 'political disease' for black people in this country. It has also been called 'a prickly disease' because of the deep emotions which surround any condition that is predominantly confined to one racial group.

The Political and Economic Issues

Now that we are able to screen pre-natally for other conditions using high technology machinery, this involves costs and we have to be certain that we know where we are going because for the haemoglobinopathies we need to look at accesss to diagnosis and treatment. Are we going to offer pre-natal diagnosis to everyone involved and if they refuse abortion, are we going to not offer them services for the affected babies? Are we still doing it as a research project or for services for people?

The team approach should be used here beginning with community education at all levels. In many cases it is ignorance of the service rather than rejection of the procedures which keeps people away. A fragmented service without follow up is worse than no service at all.

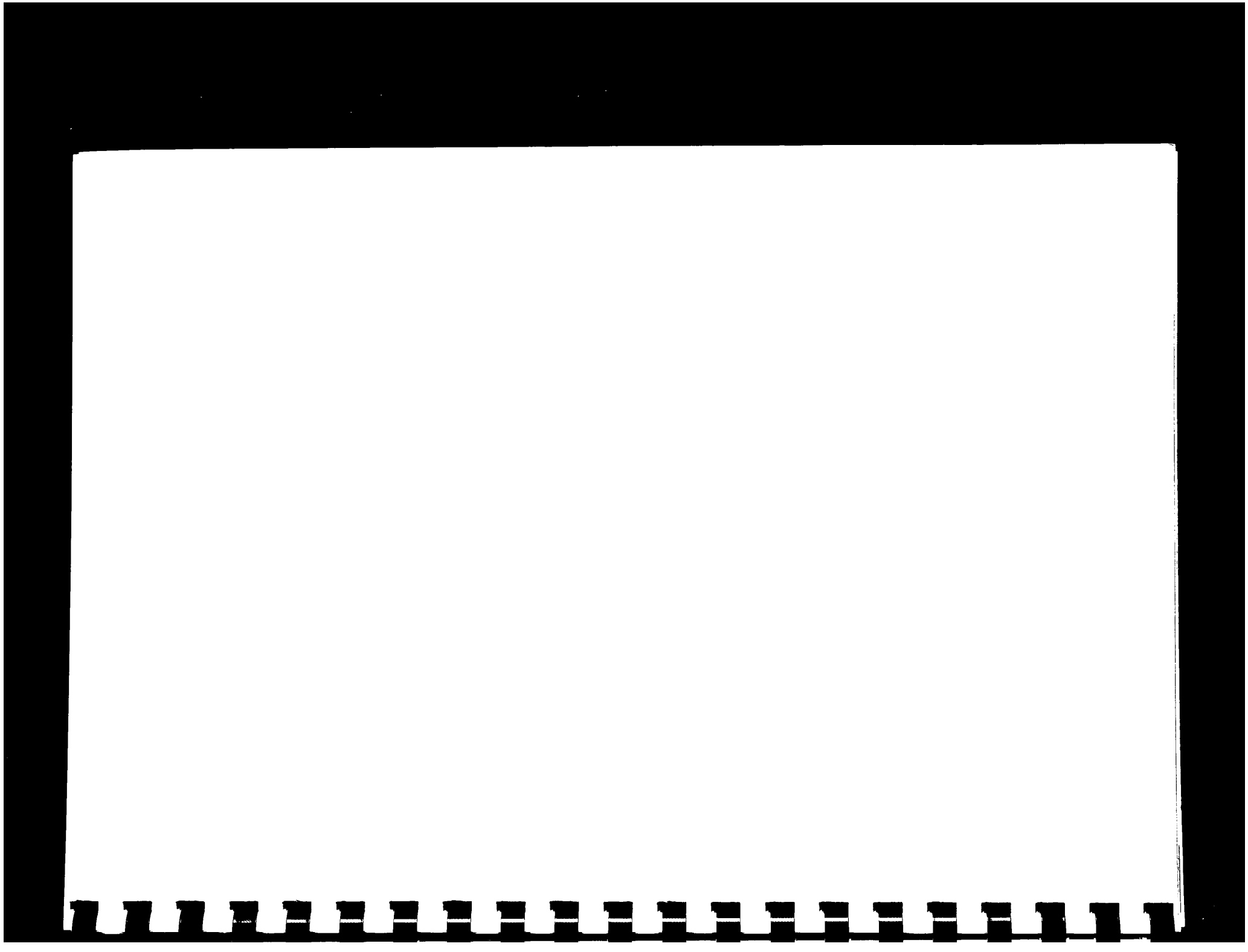
With regard to the criteria for eligibility, are we going to choose people who are educated or intelligent enough to ask for these services who we know are going to abort if the conditions are found in the fetus? Or are we going to provide proper genetic counselling services so that people can make their own decisions as to what to do for the future of thier child?

The political climate is ripe for change in that through the media we are constantly being reminded about this 'black disease' and the need for funds for prevention, education and control of these conditions.

We are aware of the crisis for funding of the National Health Service so for any new conditions the money will have to be found elsewhwere. If we are talking about saving the nation money, for example by the freeing of hospital beds, which costs roughly £150 per day in central London, we need to be aware of the prevention of these diseases, again using screening methods and our appointed leaders would have to put these facts to the government in an effort to help us to make better use of the services available at the present time.

There is a place for screening for fetal abnormality but we have to approach it carefully as to how we use the services for the benefit of our people, for example would the government turn around and say to us 'you can either have a service to prevent these babies being born or you will be denied the treatment and care for children born with these disease but you can't have both'.

There are many more questions which need to be asked and answered for the benefit of the community at large.



GENETIC PREDICTION IN HUNTINGTON'S DISEASE

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Huntington's Disease (HD) is an automsomal dominant disorder which causes chorea and dementia. The age of onset ranges from 5 to 75 years, but is usually between the ages of 25 and 60. The disease develops insidiously, with subtle fidgety choreiform movements and personality change, but the involuntary movements later impede normal motor function, giving rise to dysarthria, dysphagia, clumsiness, a lurching gait, amd progressive immobility; intellectual decline becomes obvious, and there is general physical debility. The average duration of the disease from onset to death is 15 years (Hayden 1981).

HD imposes a considerable burden upon families in which it occurs. As well as living with, and caring for, affected inviduals, the genetic nature of the disorder means that for every patient there are about eight times as many subjects at high risk (greater than 1/10) of developing the disease. Cases of HD due to new mutation are exceedingly rare.

The psycholgical burden of being at risk for HD is enhanced by the late age of onset of the disease. The risk to children of patients does not fall significantly below 50% until after their childbearing years are over, so they have great difficulties in making reproductive decisions, as well as living with uncertainty about their own future throughout much of adult life. Early 'tests' for potential gene carriers, were not reliable. Since 1983, the identification of a polymorphic DNA sequence linked to the HD gene on the short arm of chromosome 4, theoretically allows preclinical and prenatal identification of gene carriers (Gusella et al 1983). If applied on a large scale, there is a real opportiunity to reassure much more than half the 20,000 at risk who are living (as many have less than a 50% risk of carrying the HD gene), and to reduce the incidence of the disease in future generations. There is, nevertheless, a number of practical and ethical difficulties.

Crauford and Harris (1986) have recently identified three areas for concern in relation to predictive testing in adults at risk of developing HD: the possibility of inaccurate prediction; the psychological burden of being identified as a gene carrier; and the possible misuse of information gained from predictive testing. Inacuracy may arise from recombination, the seemingly small possibility of locus heterogeneity in HD, and misdiagnosis. This small possibility has the advantage of leaving a little hope for those predicted to have a high risk of carrying the HD gene.

There is increased incidence of psychiatric morbidity and suicide amongst HD families. It is unclear whether this is related to the stress of being at risk, the effects of the gene itself, or the disrupted home environment which is so frequent. It has been suggested that individuals at risk who are shown to carry the gene will be at increased risk of suicide and depression, but this presupposes that other factors are relatively unimportant. Currently we do not know what the psycholgical effects of predicting the development of HD, an untreatable disease, will be. The benefit of reassuring considerably more than half of those at risk, and presumably reducing psychiatric morbidity in them, must be entered into the equation.

Adults requesting genetic prediction should be made aware of all the implications of the results. Testing may not be wanted by all members of the family, making it impossible to test others that do. Identificaiton of some gene carriers will increase risks for their near relatives who might not want to know that this is the case. Present or potential spouses may want to know when the person at risk does not. The same applies to employerrs and insurance companies. It is clear that the clinical application of predictive testing for HD and other inherited diseases is not predominantly a laboratory issue. HD has special problems and presymptomatic testing should not be undertaken in centres unable to provide continued support for those shown to have a high risk of carrying the gene.

Apart from ethical considerations and the practical problems imposed by the nature of any linked marker, it seems that the main factor limiting the use of D4S10 in clinical practice is the fact that most HD families are fragmented, with few key individuals available for testing. In order to determine which D4S10 haplotype is segregating with the HD gene in a given family, it is necessary to test at least two generations containing affected individuals. For practical purposes this means that for genetic preduction in an adult at risk (ie with an affected parent), there must be at least one parent and grandparent (affected or unaffected) available for testing. A population based study of HD families in South Wales suggested that presymptomatic prediction would only be possible in about 15 per cent of adults at risk, as the majority did not have surviving grandparents (Harper and Sarfarazi 1985). However, 36 per cent od adults attending the National Hospital genetic clinic with a 1 in 4 or greater risk of developing HD had the minimum pedigree structure required for presymptomatic testing using linked genetic markers (Misra et al, unpublished data).

Both of these studies indicated that genetic prediction would be possible in about 90 per cent of pregnancies of these adults at risk, allowing virtual exclusion of HD in half of them and predicting a 50 per cent risk of carrying the HD gene in the other half. This approach does not alter the paren's risk in any way, which has certain advantages in view of the ethical problems generated by presymptomatic testing of adults, and the fact that 10-40% of adults at risk do not 'want to know'. Pregnancies at high risk can be terminated in the first trimester. Ethical objections may be raised at the prospect of termination for a late onset disorder when the fetus has a 50% chance of being normal, but termination of lower risk pregnancies is not infrequent at present.

The economic burden of HD is considerable. About 50% of patients require long term hospital care, with an average duration of four years. The minimum lifetime cost of one patient was estimated as £20,00 in 1979, excluding loss of his or her earnings, support to families from social services, or the cost of psychiatric morbidity in relatives at risk (Tyler and Harper 1983). It has been estimated that there are 3,000 patients with HD in the UK and 20,000 individuals at high risk (Harper 1983). The cost of chronic institutional care alone for HD in the UK is at least 6 million per annum (400 patients in residential care at any one time), and the real annual costs of the disease must approach 10 million.

The establishment of screening programmes for HD will be a highly cost effective exercise, even though the investment is rather a long term one; the savings resulting from reducing the incidence of the disease by 10% would pay for the laboratory and paramedical counselling services needed to screen the population at risk.

GENETIC RISK

Stephen Thomas
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The panel's five questions are considered with particular reference to Huntington's chorea (HC), highlighting some of the dilemmas which face HC families. I then look beyond the particular case of Huntington's chorea and make two recommendations which are not narrowly disease-specific.

Professional diagnosis of HC is often difficult. Mistakes are made. Diagnosis error has profound consequences for the mis-diagnosed person and his or her family.

DNA marker (G8) doesn't banish the problem of diagnostic accuracy. Whether used as a so-called 'exclusion' test in pregnancy, or as a pre-symptomatic predictive test for an individual at risk for HC, the marker's informativeness depends on there being at least one accurate diagnosis of HC.

The HC gene itself hasn't been identified. Another King's Fund Forum would be needed to consider the implications of such a discovery.

Diagnosis is often impossible in the initial stages. By the time a history of sad decline is recognised as HC, the affected person may well have children.

Try to imagine the burden on the family if (a) the affected person is advised that he or she is in the grip of a progressive incurable disease; (b) the spouse learns that the affected person is being killed and changed by degrees; (c) both of them learn that their two children are each at 50% risk of having the HC gene; (d) both of them learn that the affected person's brother who committed suicide, had HC.

Diagnosis in this case has come too late to constitute a shield between generation I and generation II. There are two young children. None, one or both of these children may turn out to have the gene.

<u>Benefits of being told as soon as possible (or early) about HC and risks:</u>

Early sympathy and understanding within the family, workplace, neighbourhood. Early medical treatment for some symptoms, e.g. involuntary movements. Early practical, financial and social preparation. Less demanding job. Help for the spouse or family carers. Reduce sense of isolation and increase hope of cure through e.g. Association to Combat Huntington's Chorea. Knowledge of research efforts. Consider arranging for brain e.g. to be studied after death.

Reduce the 'if only I'd been told earlier' resentment against doctors. Use a priori 50%/25% risk estimates to allow generation II to make 'informed' decisions about jobs, careers, finance, marriage and procreation. Warn girl-friends and boy-friends of what they may be taking on. If 'at-risk' decides against producing offspring, then he or she doesn't pass a copy (or more) of the gene to next generation.

At-risk may consider using AID or donated egg to minimise risk of passing HC gene to next generation, or marry someone who already has children.

Couples with one partner at 50% risk may be able to use pregnancy tests and decide to abort if the fetus is shown to be at about 50% risk (?or 25% risk where test uninformative) but continue a pregnancy if the risk to the fetus is reduced to about 2.5%. Useful for people who without pregnancy test would not have had children of their own and for whom predictive testing is unavailable or unacceptable. Expect less stress, more joy, bringing a 2.5% risk child up. Possibly easier for the unaffected spouse of someone who develops HC - the existence of children at 2.5% risk gives hope for the future.

Only a minority of adults have the family structure required for a presymptomatic prediction test. Only a minority can learn now that there's a 96% risk developing the disease; or, say, a 96% chance of avoiding it. (The figures depend partly on family structure and won't be 96% in every case).

Benefit, for some adults, of leaving the exhaustingly unstable ambiguous status of 50-50 risk.

<u>Costs of being told as soon as possible about HC and risks</u>

Anxiety, guilt, anger, denial, depression, suicide. Everything can be blamed too early or groundlessly (as it later transpires) on HC. Despair - why bother to be an apprentice? Isolation within family. Social Isolation. Jobs loss.

Symptom-searching. Lack of confidence. Ambiguous health status makes major life decisions difficult. Some who are deterred from procreation, or who consider 'second preference' methods of producing children (AID or donated egg) don't in fact have the gene.

Difficult to e.g. sterilise oneself as a precaution and still maintain the belief that one is well.

Stressful decisions about prenatal tests and abortion. Stressful experience of pregnancy tests, abortion. Post-abortion grief for a fetus which may not in fact have carried the gene.

Those told by presymptomative test that there's about 96% chance of HC must live with uncertainty about when will it come, what will be the worst symptoms?

Having learned to live on the basis of 50-50%, may be difficult to adjust to say 96% OK, or 96% gene carrier. 96% certain gene carrier may still want untested or tested children of his or her own.

Uncertainty about what chance of onset-delay technique being developed in one's own lifetime?

What chance of effective cure or onset delay being developed in children's lifetime?

Ignorance or partial knowledge may exist in undiagnosed families. controversial to provide mendelian risk figures while there is no cure and no impressively effective means of treatment. Using the G8 marker in pregnancy, or in a presympotomatic predictive test, is also controversial.

A reduction in fertility of 'high' risk children has been reported in South Wales following outreach genetic counselling (intended to be non-directive) to all at-risk over 18 years.

For technical reasons, most but not all adults can use the pregnancy test; and only a minority can use the presymptomatic predictive test.

The South Wales centre suggests that couples considering exclusion tests should have DNA typed on relevant family members before conception.

'If the fetus inherits the G8 haplotype from the affected side of the family, its risk becomes the same as that of the parent. If termination of pregnancy subsequently became unacceptable depsite an adverse result and HD subsequently developed in the parent in generation II it would be immediately known that HD would also be likely to arise in the offspring since their risks are the same (apart from the possibility of recombination)'. In an attempt to avoid this complication, couples in South Wales are told that if termination of pregnancy is unnacceptable for whatever reason, then an exclusion test is inappropriate. But eventually someone will change his or her mind, and the complication will arise.

Prenatal exclusion test involves abortion at about 50% or 25% fetal risk.

Do family members have a right not to provide their blood so that another relative cannot obtain crucial information for marker test?

Does at-risk family member have the right to know the result of test on relative.

Does a not-at-risk spouse have the right to know results of test on partner?

Does not-at-risk spouse have a right to coerce at-risk partner to undergo test (so spouse knows what she's likely to be taking on)?

Fresh mutations occur, so not even the most vigorous 'high-risk screening' would eliminate the gene and the disease. If invent onset delay (and/or cure) gene will continue, needing medical intervention generation after generation. But the gene won't suddenly sink Britain - at present about 3000 people are affected. Of the 20,000 or so estimated to be at 'high' risk, only a minority actually carry the gene.

Only a probe for the gene itself would make it feasible to predict for an isolated subject without studying the family unit. Even then, science is still very limited in respect of positive results. Could liberate negatives. But positives still left to wonder: "When will the first symptoms appear?" Modify gene's action?

Most people find life on the basis of mendelian risk figures (50% risk or 25% risk, modified in some cases to take account of age and/or sex of affected parent) stressful, and many (though by no means all) believe that less uncertainty would be preferable, both in day-to-day living and in important life decisions (job, career, marriage, procreation).

Polled shortly before the G8 discovery, about 56% (ie 51 people) of a Soouth Wales group who were at-risk expressed a wish to take a predictive test if one existed.

The wishes of those wanting to leave the cauldron of 50-50 risk for the new world of say 4% or say 96% risk should be respected.

The wishes of those who want to stay in the a priori cauldron should also be respected. It takes time to learn to cope psychologically with 50-50 risk. A pay-off is hope.

Proportion of 'fresh' mutations hard to estimate, but generally agreed to be lower than in many other diseases.

Genetic counselling, prenatal 'exclusion' tests, and presymptomatic predictive tests may reduce the rate at which the gene is transmitted. This in itself is not a solution. What families desperately need now is a cure or radically improved means of treating the disease, or even the means of delaying onset.

Organisation

The funding of regional genetic counselling services and G8 tests should not be made conditional on regional centres achieving a reduction of so-called 'high risk' conceptions and births. Tests should be voluntary. Protect, so far as possible, both right to know and right not to know.

Psychological support should be an integral part of the information system, also pre-test and post-result counselling. If a test centre has a policy of unauthorised disclosure of results (eg to employer) must declare it on consent form before getting blood samples. Before members of a family give blood samples, helpful if they are asked whether they consent to make information available to relatives.

Spouses, especially if parents and the offspring of symptomatic or asymptomatic parents have a prima facie right to know results in order to make informed decisions. Relative wanting information, provided affected person and his/her immediate family have consented to make information available to other relatives, has right to information. Confidentiality of test results should be safeguarded and test centres should be accountable to those not wanting to know test results.

Monitoring performance of HC Screening Programme

People from outside each regional centre to help assess customer satisfaction. HC families often feel vulnerable - hard for some to complain. Some assessors should be people with misgivings about the wisdom of counselling and testing before we have a cure. Suicides should be recorded. And monitor (a) time taken to get result from CVS or other sample; (b) time taken to communicate result to clients; (c) time taken to arrange termination if termination wanted; (d) laboratory error; (e) accuracy of predictions.

Two General Recommendations

Professional estimates of genetic risks should be written down on paper and given to individuals/couples.

If the evaluative term 'high-risk' or 'low risk' is used, the written estimate should disclose the figures which form (part of) the basis of the professional evaluation.

SOCIAL AND ETHICAL ISSUES

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University of Exeter

Definitions

'Screening' - any procedures undertaken in order to detect presymptomatic disease in a population.

'Genetic Screening' - the main purpose of medical genetics (which) is to apply the principles of genetics to the practice of medicine so that the burden of genetic disorders can be reduced in the community. (M A Ferguson Smith, 1987)

I limit the discussion of screening to patients for whom there are already indications of risk. The relvant moral reasoning requires the holding in tension of a cluser of principles, each exerting moral claims. I reduce these to three.

1.1 The tension between human liberty and responsibility within nature and biological processes.

In the glib language of today's pseudo-piety medical scientists are alleged to 'play god'. If this is meant to imply that only God, as Creator of nature, may manipulate it, the slogan is absurd. It has no foundation either in theology or in human experience. Theology, with its language of man made in the image of this Creator God, attributes responsibility to man, a limited dominion, within the created order. Millenia of human experience, from animal husbandry and agriculture to medical practice, had recognised human intervention as a timeless and universal human activity proper to the nature of man. God is neither jealous nor mocked.

Nature is neither devine, perfect nor immutable. In the realms of human biology its products from time to time are marred. A combination of scientific disciplines now yields, first, some understanding of how these mishapes occur; secondly, means of detecting some of them antenatally, at even earlier stages of development; and, thirdly, means to remedy or palliate some few of those detected. It would be hard to establish a reasoned moral case forbidding the exercise, in this field, of normal human faculties to protect human kind from the random adversities of nature.

2.1 The tension between human liberty and responsibility with human life.

Concomitant with genetic screening goes the option of terminating the life of a defective conceptus. Technical progress offers that option both more extensively and ever earlier - from fetal scanning and amniocentesis late in pregnancy, to chorion villus sampling at the

transition from embryo to fetus, back to cellular biopsy and analysis during pre-embryonic cleavage; with DNA technology adding remarkably to precision. A defective pre-embryo need not to be implanted; a defective embryo or fetus may be aborted: the choice lies with the mother, clinically advised.

All responsible participants in this debate hold human life to be sacred in the sense that it is of paramount worth, and that it has claims to care and protection, and to service in its vital interests. Some go further and interpret 'sacred' to mean inviolable. They would prohibit as a moral wrong the arrested development of any pre-embryo and any termination of the duty of loving care for the handicapped, with the consequent loss of reciprocated warm human relationship with them. Others, without weakening in resolve to care for the handicapped if born, or in appreciation of the depth of affectional relationship possible with them, would still maintain the option of their not being born, partly in their own assumed interest, partly out of an estimation of the capacity or incapacty of their parents or of society to give them that optimal care. They would regard the prospect of severe congenital handicap as an indication strong enough to rebut the accepted presumption in favour of life.

3.1 The tension between human liberty and responsibility in relation to persons in society.

Medical genetics shares with most medical practice the primary obligation to each patient, one by one: to a person, in strict terms the bearer of rights, and more generally the embodiment of interests to be enhanced and enjoyed. The patient is also a member of a body corporate, a human society in its various cellular structures - blood group, family, kindred, nation, race, and so on. As a social morality grows out of a tension between personal interests and corporate or social interests, so an ethics of medical genetics has to take account of the social consequences of accumulated clinical decisions made primarily in the interest of individual patients. In an ethically harmonious society, and when scientific development is slow enough to carry with it a general understanding and acceptance, that tension between the personal and corporate will resolve itself in conventions, norm of conduct, professionally and socially accepted. When these two conditions - ethical homogenuity and a manageable tempo - are lacking, as they are today, conflict is inevitable. Resort is had to law, either through the courts or in parliament, as those fearful for the common good, or for their own absolutist standards of morality, seek to restrain the liberty of those who attach wider options to their professional responsibility. There is also the other fear that governments, or the tyranny of television or other medical pressure, will override personal liberty and impose screening and termination on those who would not choose it.

Do I err greatly in seeking to locate our ethical discussion within these three fields of choice or tension? If not, let us see into which field or fields some of the empirical features of prctice fall.

1.2 Our understanding of man's place and limited dominion within nature entails an obligation to pursue scientific enquiry and the beneficial application of its results. Disciplined curiosity and the liberty to pursue fundamental research are to be affirmed. There is ample encouragement to go forward, evidenced especially by DNA technology. For example, affected male haemophiliacs can be identified by this means from CV samples or later, so that no normal male need be terminated - a notable advance on the old 50% gamble. Similarly with Duchenne muscular dystrophy: with the multiplication of gene probes only 1% of families are not amenable to identificaiton. Carrier and non-carrier females can be distinguished.

Work on single embryonic cells from pre-implantation mouse embyros indicates the possibility of identifying in human pre-embyros the HRPT deficiency for couples at risk of having children with Lesch-Nyhan syndrome (Monk et al, Lancet August 22, 1987). These are examples of research which yields an ethically valuable economy in the sparing of fetal life, in reducing the trauma of late abortion, and - if pre-implantation diagnosis, despite its higher cost, can go forward- a pointing of the way to obviate, for certain diseases, termination of pregnancy altogether.

But modesty of expectation must yet prevail. There is no prospect, either theoretical or practical, of ultimate certainty in these matters - it is not simply a question of diagnostic error. Random in evolution must elude control. Enough is known to rule out the possibility of those spectral powers attributed to geneticists of fabricating men after their chosen image. It is ethically necessary to explode false expectations of this sort. I learn from my friend the Chief Rabbi that Jewish Orthodoxy would support what he would call 'repair' genetics, to eliminate when possible the expression of deleterious genes in human bodies. What Jewish Orthodoxy dreads is the spectre of the superman or super race, genetically fashioned. If that is, as I believe, beyond possibility as well as intent, let it be said.

Equally, the power inherent in medical genetics must be preserved from abuse in trivial causes. Martin Richards has spoken of 'the camel's nose'. The threat is not only that our concept of the tolerable in handicap should diminish to the point where our humanity is diminished with it. It is also that the human will should intrude too far: to aborting a child of the unwanted sex, for instance, without the justification of a sex-linked disorder. The responsibility of genetic counsellors is serious here. The price of liberty must be self-restraint from the frivolous and the bizarre.

2.2 What has just been said about the use of our liberty within the natural process has sharper definition in relation to our responsibility for human life. This is not an occasion to rehearse the old abortion debate. We work, anyhow, on the fringe of that problem: only a small percentage of terminations are registered on the ground of fetal handicap.

The leading fact is that nature itself discards spontaneously some of its defective products. Unfortunately, being as uncertain in its calculations as we are - if not more so - it does not discard them all. Neither is there, beyond a certain point, any exemplary scale of what it discards: some of those which it spares are amongst the most gravely handicapped. Furthermore (except in conditions fatal before puberty) nature seems not to check the descent of defective genes from generation to generation - which is one of the goals (with recognised limitations) of medical genetics. The question then follows: if genetic screening with selective abortion is in fact a rationalised adjunct to natural processes, are there ethical controls to guide it?

It seems to me that once we repudiate (as I must) the absolutist prohibition on abortion, the ethics must be wrought in a continual tension between a general presumption in favour of life and the strength of a claim to rebut it in any particular case. The claim must not be trivial if it is to prevail: and it should have respect for human life in its relational capacity as well as in its biological reality. And the solution may well be worked out in a tension between the genetic counsellor and the potential parent - the one sharing something of a professional ethics in the matter, the other something of the wide spectrum of attitudes current in our society.

I suggest further that we only make the task harder if we pose the problem in the language of a conflict of rights. In hard fact, the fetus has no rights, as the law and hard reasoning, understand rights, until it is born alive. And English law does not confer on any woman the right to an abortion: the Statute of 1967 defined conditions in which the termination of pregnancy would not be a criminal act. Progress would look more promising, I believe, if within the concept of a duty owed to the unborn child by both parents and physician - for duties can stand without the supposition of rights - the ethics are sought in a weighing of <u>interests,</u> those of the unborn child and those of the mother, and a consideration of how these interests are to be served, whether together or one at the expense of the other. One interest clearly to be served by genetic screening is that of a potential mother in an assurance, if it can be given that her next child should be normal.

3.2 We pass finally to the tension between individual persons, whether physicians or patients, and the society of which both are members.

The science of medical genetics and gene mapping now carry the study out into the patient's family, whose cooperation has to be won. Here again the language of rights will prove unhelpful. Human <u>wills</u> are involved, and they have to been wooed and won to serve the relevant interests. But the search requires the sharing of knowledge gained in a clinical relationship; and here we meet the old questions, how much must be kept secret? How much may be told? How much should be told? Let us take this step by step.

The House of Lords in Sidaway established the duty of a physician to give information as would enable a patient to consent or not, to any medical procedure proposed for him. I doubt whether that duty extends to giving a patient all information gained in clinical investigation, and particularly when no medical intervention is indicated. It is often asked, has the doctor a duty to disclose the sex of a fetus antenatally determined? If the context were genetic counselling in relation to a sex-linked disorder, the obligation to tell would seem clear: disclosure is relevant to a vital interest of the mother and of the unborn child. But where the interest is trivial or non-existent, the obligation, I would say, diminishes; it must remain discretionary. It would be hard to sustain a right to know and a duty to disclose the sex of the fetus simply in order for termination to be sought if it were not of the sex preferred. A multiplication of such terminations is likely to have social consequence in an imbalanced population structure, either absolutely between the sexes or timewise in order of births. In some cultures that likelihood amounts to certainty. The social interest or common good must prevail against personal whim.

Next: a patient has an interest in the non-disclosure of genetic information to third parties - in relation, perhaps, to employment, insurance, social stigma and the like. Without consent such disclosure would be unethical. But genetic disorder is not strictly a personal matter only. It has ramifications for siblings and consequences for future generations. It touches also the social interest in the health of a population. Without some sharing of information the genetic mapping of families cannot be undertaken.

The language of rights is useless again. We are left with an obligation, first to establish trust between the patient and the medical geneticist, and confidence in the operation; and than to seek for willed consent to such disclosure as, step by step, will aid the serving of all the interests involved, personal and social, as they emerge.

Fundamental to medical genetics is what we call truth. The more the study moves out from the individual to the family, the more important is the assumption that social identity - who we believe we are - coincides with genetic identity, who genetically we are. (Uncertainly of parentage arising from human waywardness is morally irrelevant). If this be so, is it not time to call into question the insistence on anonymity for donors of gametes in the medical remedying of infertility? And to press for methods of registration which, while tolerant of acceptable fiction for those who want it, will enable fact to be disclosed to those who need it? If we believe in any coherence between rationality in science and moral rationality, not only medical disciplines in their complementary but also social policies in their consistency should be grounded in what science professes to seek: truth.

ORGANISING SCREENING PROGRAMMES FOR THE NEW GENETIC TECHNIQUES

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The new genetics (recombinant DNA technology, rDNA) represents arguably the greatest challenge that clinical medicine has yet faced. In addition to the rapid introduction of rDNA into family screening, it is not difficult to envisage proposals within the next few years for general screening for important genetic and chromosomal disorders including routine chorion villus sampling. Environmental engineering will also be advocated for those found to have a strong genetic predisposition to common diseases. Current rDNA methods are very successful for family based 'gene tracking' but are generally unsuitable for carriers detection in the population. However, it is clear that we are entering an era of population screening using new rDNA techniques, notably oligonucleotide probes and DNA thermal amplification. The same methods may greatly simplify family screening. Additionally the isolation of gene products may allow primary screening by simple biochemical means.

Rapid changes in technology are therefore likely and a range of different approaches for different diseases may be needed. The immediate prospect is for rapidly escalating demands as new diseases become accessible to the new genetics. For mendelian disorders this demand has two phases, a catching up phase during which the large backlog of families is cleared. The second phase which follows will probably be less intense as the number of new cases of even the commonest mendelian disease is relatively small (only 350 new cases each year of cystic fibrosis, or about 25 in each Health Service Region). However, future demands cannot yet be predicted from population screening and rDNA applications to common disease (vascular, diabetes, cancer etc).

These uncertainties indicate the need for a limited number of laboratories working closely with clinical geneticists and having the appropriate experience and resources to act as test beds for new procedures, introducing limited services as they are evaluated. This will allow time for considered decisions on the location, distribution and type of technology required. Familiarity with a particular technique, probe and disease requires specialisation especially for rare disorders and an adequate throughput is necessary to maintain this familiarity and to ensure training needs.

The costs are modest, in comparison to the potential savings and benefits although it would be extremely inefficient if there was a plethora of small rDNA laboratories at a time of rapid change.

Public awareness, education and acceptance, genetic counselling, informed consent and confidentiality must be considered before screening can be initiated.

Table 1 Incomplete List of mapped Genetic Diseases (Aug 1987)

Adrenal Hyperplasia, Cong	Myotonic dystrophy
Adult Polycystic Kidney disease	Norrie's disease
Cystic fibrosis	Phenylketonuria
Duchenne/Becker Musc Dyst	Prader-Willi syndrome
Familial adenomatous polyposis	Retinitis pigmentosa
Fragile X	Retinoblastoma
Haemochromatosis	Sickle cell anaemia
Haemophilia A	Thalassaemias
Haemophilia B	Tuberous sclerosis
Huntington's chorea	Von Recklinghausen's
Hypercholesterolaemia, familial	Wilms tumour
Lesch-Nyhan syndrome	

Table 2
Costs of Establishing and Running a Basic rDNA Laboratory as part of an Existing Regional Genetic Service (1986 prices rounded)

Capital	£
Basic Equipment	80,000.00
Recurrent	**£**
Staff Salaries	73,000.00
Non-Staff Revenue (consumables)	36,000.00
Replacement/repair	8,000.00
Total (annually)	£117,000.00

(No allowance for knock on costs for other Specialties notably Obstetrics and Diagnostic Ultrasound or for overheads, heat, lighting etc.)

THE FUTURE

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Over the last few years enough information has been collected to indicate that carrier detection and first trimester prenatal diagnosis by DNA analysis is a feasible and increasingly valuable approach to the control of monogenic disorders. Several technical developments are well advanced which will facilitate the clinical application of DNA technology. For example, provided the economic and organisational problems can be overcome there seems little doubt that we shall have a complete genetic and probably physical map of the human genome within the forseeable future. A complete sequence of the human genome is now not beyond our reach. This will facilitate the pinpointing of genes for important diseases. Furthermore the technology for gene analysis is being simplified and within the next ten years should be within the grasp of most clinical laboratories both in the developed and developing world. There is also a considerable interest in the possibility of taking prenatal diagnosis back to DNA analysis of fertilised eggs although it is my personal view that this approach is unlikely ever to be as cost-effective as chorion villus sampling.

For the clinical application of DNA technology for the secondary prevention of monogenic disease to be successful the major difficulty will be organisational rather than technical. We shall have to launch a major programme of education for both the public and their doctors. This will have to be carried out with great care because the medical profession itself now is still not conversant with the possibilities of the new genetics and in a society which is increasingly aware of cost-effectiveness it is going to be particularly important to make sure that once the possibilities of the control of genetic disease are widely understood there is no governmental pressure put on populations to undergo genetic screening and wide-scale prenatal diagnosis; there must be no return to the (heady) days of the eugenics movement earlier this century.

What of the long-term future? We shall have the ability to identify the bulk of important monogenic diseases. I suspect that the next step will be the ability to identify submicroscopic lesions of the chromosomes which underlie at least some hitherto unexplained forms of developmental abnormalities. Undoubtedly we shall identify the genes involved in human development and understand better how they can interact with the environment to produce congenital anomalies. Thus I suspect that we will slowly move towards a better understanding and ability to prevent these conditions and the next stage will be the elucidation of the genetic component of common polygenic diseases such as heart disease, diabetes, psychiatric disease and so on. From a practical point of view this should ultimately enable us to define particularly high risk groups of individuals for the effects of environmental factors such as diet, smoking, common viral infection and so on. But this work willgo much more slowly and I suspect these practical benefits will not be available for many years yet.

Similarly, it seems likely that we will gradually learn how to replace defective genes and therefore our approach to the control of genetic disease may change from termination of pregnancy to early identification of these diseases for purposes of therapy. But again I think there will be a long time before this happens and for many years our major efforts will be directed towards the identification of couples at risk for carrying serious genetic disorders followed by the offer of termination of affected pregnancies.

The type of technology that is being discussed seems likely to revolutionise medical research and medical practice over the next 100 years. To reap full benefit from these advances we shall require a complete rethink about the training and organisation of the medical profession. At the same time we shall have to learn how to discuss these increasingly complex issues with our patients; the speed of advance of molecular biology has already taken the medical profession by surprise and the field is perceived as a further development of high technology medical practice. It is important to realise that it is not; the long-term benefits are likely to be in the area of preventative medicine and definitive therapy rather than high technology patch-up procedures which are the hallmark of the medical care in advanced countries at the present time.