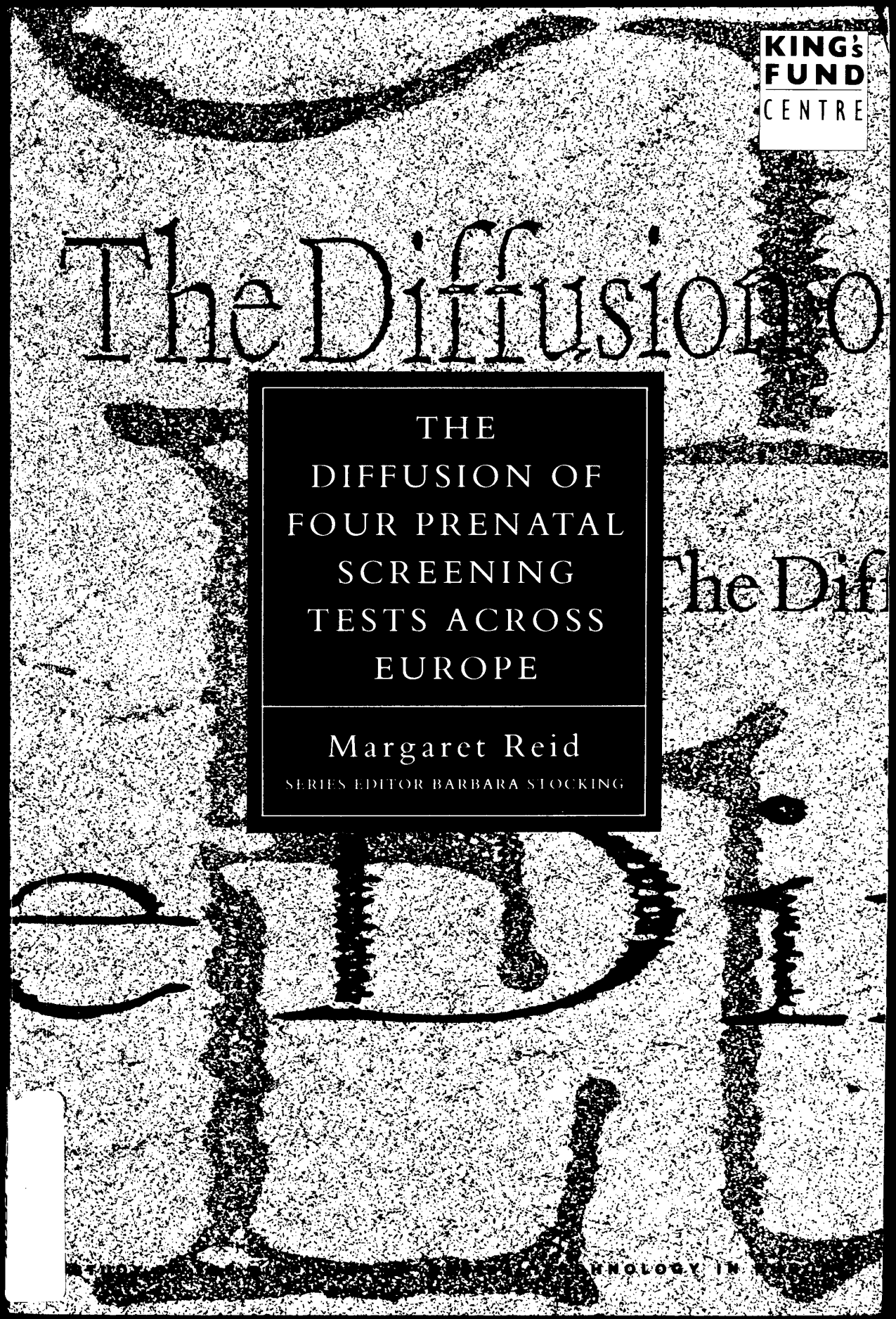
KING's FUND CENTRE
The Diffusion o
THE DIFFUSION OF FOUR PRENATAL SCREENING TESTS ACROSS EUROPE
Margaret Reid
SERIES EDITOR BARBARA STOCKING
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A STUDY OF THE DIFFUSION OF MEDICAL TECHNOLOGY IN EUROPE

THE DIFFUSION OF FOUR PRENATAL SCREENING TESTS ACROSS EUROPE

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Maria Feijóo, Lisbon

and based on country reports from all EC Member States and Sweden

plus

FACTORS AFFECTING THE DIFFUSION OF THREE KINDS OF INNOVATIVE MEDICAL TECHNOLOGY IN EUROPEAN COMMUNITY COUNTRIES AND SWEDEN

BARBARA STOCKING

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The King's Fund Centre is a health services development agency which promotes improvements in health and social care. We do this by working with people in health services, social services and voluntary agencies, and with the users of their services. We encourage people to try out new ideas, provide financial or practical support to new developments, and enable experiences to be shared through workshops, conferences and publications. Our aim is to ensure that good developments in health and social care are widely taken up.

The King's Fund Centre is a part of the
King Edward's Hospital Fund for London.

A STUDY OF THE DIFFUSION OF MEDICAL TECHNOLOGY IN EUROPE

How can a society afford to pay for the often expensive new technologies introduced into health care, assess their ethical and social impact, and prevent or restrict their diffusion from the innovating centres to general medical services if their drawbacks appear to outweigh their benefits? Are formal or informal regulatory mechanisms the more effective? Is diffusion easier to control in countries with predominantly public health services? Is this to patients' benefit?

In the belief that these questions would be illuminated, both for health policy makers and for the protagonists of new methods of medical treatment or disease prevention, the European Commission, via its committee COMAC HSR in DG XII, commissioned a study in each EEC country and in Sweden of the diffusion of three recently introduced technologies:

- renal stone treatment, particularly by lithotripsy
- organ transplantation, with particular focus on liver and heart transplantation
- prenatal screening, particularly for Down's syndrome and open neural tube defects.

Rapporteurs were identified for each of the countries, as well as a single author to write an overview drawing on these country reports and other material. Three of the country reports on organ transplantation are published here in addition to the overview; they were selected from those received either because they illustrate a particular factor operating strongly in that country or an unusual (or typical) diffusion pattern. Unpublished country reports are available either from me or from the EC committee named above.

The three types of technology were chosen because they have very different characteristics. Lithotripsy involves a large capital investment in an expensive machine. Organ transplantation demands the exercise of high surgical, scientific, and above all organisational skills under emergency conditions, and raises serious ethical questions. Prenatal screening uses relatively cheap materials and equipment but again raises ethical and religious problems, and draws the attention of special interest groups. The diffusion of each of the technologies is discussed in three companion volumes, of which this is one.

I attempt at the end of this volume (and in the two others) to draw some general conclusions about factors affecting the diffusion of new medical technologies, pointing to similarities and differences between the three technologies studied. The authors of the overviews, of course, discuss similarities and differences between countries within each technology.

I am grateful to the EC for funding the study, to COMAC HSR for help in identifying some country rapporteurs and particularly to Martin Buxton of Brunel University for his support throughout. Michael Bos conducted extensive correspondence with the rapporteurs for this study; thanks are due to him as well as to the rapporteurs themselves. They are listed in the Foreword. Finally, all the chapters (including mine) have benefited from the editorial skills of Peter Woodford.

Barbara Stocking, Project Leader
Director, The King's Fund Centre, London NW1

A STUDY OF THE DIFFUSION

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FOREWORD AND ACKNOWLEDGEMENTS

The introduction of prenatal screening and diagnostic tests is not simply the addition of a new technique or service. Moral, social and political decisions accompany their diffusion, and although none of the techniques requires massive technological investment, their implications for each country are large-scale, reaching far beyond the pregnant woman and the individual fetus.

Data on which this review is based derive mainly from reports received from all the EC countries (except Luxembourg, which submitted only a brief summary) and from Sweden, which was included as a participant in the EC COST (Coopération Scientifique et Technologique) programme. The list of countries and rapporteurs is given below.

Belgium: Dr C Deliens, École de Santé Publique, Université Libre de Bruxelles, 808 Route de Lennik, 1070 Brussels

Denmark: Dr J Knudsen, Danish Hospital Institute, Nyropsgade 18, 1602 Copenhagen V, and **Professor Gavin Mooney,** Health Economics Research Unit, University of Aberdeen Medical School, Foresterhill, Aberdeen AB9 2ZD

France: Dr M Briard, Hôpital Necker, 149 Rue de Sèvres, 75015 Paris

FRG: Dr I Nippert, Institut für Humangenetik, WWU Münster, Vesaliusweg 12–14, 4400 Münster

Greece: Dr C Metaxotou, St Sophia Children's Hospital, Goudi, 115 27 Athens

Ireland: Dr J Barry, Baggot Street Hospital, 18 Upper Baggot Street, Dublin 4

Italy: Dr E Terzian, Sezione di Epidemiologia, Istituto di Technologie Biomediche Avanzate, Via Ampère, 20131 Milan

The Netherlands: Dr G Engel, Stafbureau, Academisch Ziekenhuis, Postbox 1918, 6201BX Maastricht

Portugal: Dr M de Jesus Feijóo, Hospital Egas Moniz, Rua da Junqueira 126, 1300 Lisbon

Spain: Dr J Calaf, Hospital de la Santa Creu, 1 Sant Pau, Servei de Ginecologica i Obstetricia, Avgd. S.Antoni M Claret 167, Barcelona

United Kingdom: Dr J Spiby, North West Thames Regional Health Authority, 40 Eastbourne Terrace, London W2 3QR

Sweden: Dr G Lindmark, Department of Obstetrics and Gynecology, Akademisch sjukhuset, Uppsala Universitet, S–751 85 Uppsala.

The country reports published at the end of this review, and in the accompanying volumes dealing with lithotripsy and organ transplantation, were selected as representatives of all the countries surveyed, but also to illustrate some of the specific influences covering each technology. In this volume, reports are included from the Federal Republic of Germany (FRG), Portugal, Sweden and Greece.

The *FRG* report illustrates the influence of the providers of prenatal diagnostic services: geneticists, paediatricians and obstetricians who successfully lobbied health care decision makers at state and federal government level. They did so in a country where human genetics had been totally discredited by its use by the Nazi state and where even at present some groups still have reservations concerning prenatal genetic diagnosis.

The report from *Portugal* describes the influence of abortion laws, the attitude of the Catholic church and of many Catholic doctors towards abortion including that of defective fetuses, and the comparatively recent liberalisation of public expression on ethical and social issues. There is no official policy of screening for fetal disorder. Access to prenatal diagnosis is limited by a lack of public awareness and lack of cooperation by a proportion of referring doctors.

The *Swedish* report was included because Sweden was one of the first countries to introduce fetal chromosome analysis by amniocentesis in the early 1970s. Despite the fact that no formal central decision has been taken on its use, there is remarkable uniformity across the country in the indications used and the degree of acceptance. Chorionic villus sampling was recently introduced in Sweden and is expected to be soon the commonest way of obtaining samples of fetal chromosomes. In contrast, there has been a generally negative attitude towards AFP screening for the diagnosis of neural tube defects.

The *Greek* report illustrates the importance of a change in the abortion laws before prenatal diagnosis could diffuse widely. There is, however, still limited capacity in Greece, and more than half of all cases for amniocentesis come from Greater Athens. As well as the factor of ease or difficulty of geographic access, the report also provides evidence of the effects of general educational level of the population on requests for prenatal diagnosis.

Besides the country rapporteurs, thanks are also due to the following for their willingness to discuss aspects of prenatal screening in their countries; their contribution to this review was more than significant.

Sigoline Aymé, INSERM U 242 Marseille, France.
Dr Adrian Grant, NPEU, Oxford.
Professor Laird Jackson, Thomas Jefferson University, Philadelphia, USA.
Dr Susan McManus, Dublin, Eire.
Dr Bernadette Modell, UCH London, UK.
Professor Norman Nevin, City Hospital, Belfast.
Dr Martin Richards, Child Care and Development Unit, Cambridge.
Dr David Stone, Social, Paediatric and Obstetric Research Unit, Glasgow, Scotland.
My colleagues at the Duncan Guthrie Institute for Medical Genetics, Glasgow, at UMIST and the Science and Technology Policy Dept, Manchester, UK.

Although the rapporteurs all received the same remit, the amount of raw material available about the diffusion of tests varies considerably

between countries, affecting the detail of the analysis, and in practical terms, the length of the reports. For political and economic as well as social and religious reasons, countries have in the past invested widely different resources in medical technological advances.

In some countries prenatal screening services have been expanded only recently. Because of this lack of history, and recent emergence from repressive régimes with heavy restrictions on press and consumer debate about controversial issues, some rapporteurs (for example, in Portugal and Spain) had little documented evidence upon which to draw. A 'north–south divide' already begins to emerge when we consider that, by contrast, rapporteurs from some of the northern European countries (for example FRG, The Netherlands, Sweden and the UK) had access to nearly two decades of documented material, which included professional controversy over various tests, graduate theses on the medical and social aspects of screening, and reports of media debates in newspapers and on television, with professional and consumer participation.

Countries have very different traditions regarding the collection of health-related data, and this too contributed markedly to the variability of the reports. Thus, routine statistics on a wide variety of health and social factors are readily available in Denmark, whereas the UK rapporteur had difficulty in obtaining evidence of national trends in, for example, amniocentesis screening. Indeed, the lack of standardisation in the collection of health service statistics means that comparability between EC countries is, at best, imperfect. This review refers to data where accessible, but the lack of routinely collected reliable public health service data plus the unknown quantity of private sector practice results in only a partial understanding of diffusion practice. This is most noticeable for Italy.

Ireland (Eire), where abortion is illegal, receives little more than passing mention. Unlike in Belgium, an EC country where abortion was illegal until very recently, the Irish law is strictly upheld. The Irish rapporteur did no more than offer a brief description of the situation as it currently exists.

Finally, this review is concerned with the diffusion of screening tests specifically within the EC. The role of 'silent partner' which the USA plays in this report does not reflect its actual role as a more interactive and at times pioneering colleague.

What does emerge from the reports is a story of a highly dynamic field, where the status and importance of tests has fluctuated over the years. It is a story without a conclusion, for at the time of writing the situation is fluid, with the possibility of a decline in one test and more than a suggestion of the reappraisal of another. We are, then, reviewing the field of prenatal diagnosis early in the innovation cycle and before techniques and approaches have stabilised – presenting, therefore, an account of the diffusion of four screening tests with all the limitations of today's vision.

1 SUMMARY AND DEFINITIONS

This review describes the diffusion of four prenatal screening tests into eleven EC countries, plus Sweden, which has been included as a country participating in the EC COST (Coopération Scientifique et Technologique) programme. Virtually no prenatal screening is carried out in Ireland. The four tests – amniocentesis with chromosomal analysis, chorionic villus sampling, ultrasonography and maternal serum alpha-fetoprotein determination – aim at detecting fetuses with Down's syndrome or a neural tube defect, although they have other applications.

The pattern of diffusion traced from accounts by rapporteurs in each country charts the introduction of the test and its subsequent promotion. Whilst many differences emerge, the diffusion of prenatal screening tests is seen to be affected by three significant common factors: the importance of religion, the dependence on physicians' and consumers' knowledge and attitudes, and the degree of control exercised by governments over development of the service.

The degrees of diffusion of the four tests are shown to be interrelated, and although all have achieved acceptance into the genetic service in many EC countries, the future of none is certain. This review identifies the benefits and uncertainties associated with each test and describes the debates within the field which have affected the process of acceptance of each test.

A further general pattern can be discerned: that of a north–south divide across Europe, crudely seen as a difference between early and late innovators, although the situation is undoubtedly more complex than this simple distinction would indicate.

Definitions

Before we consider each of the tests, it is important to review briefly the terms 'screening' and 'diagnosis'. Although the general title of the project was prenatal *screening* tests, in fact much of the discussion will focus upon *diagnostic* tests. The rapporteurs offered various definitions of the two terms. I shall settle on a fairly simple definition, but indicate its limitations. *Screening* is the identification among apparently healthy individuals of those who are sufficiently at risk of a particular disorder to justify a subsequent test or procedure.[1] Screening is often performed by means of a test, but other ways of screening a population, for example by age, are also possible. *Diagnosis* is undertaken to determine whether those considered to be at risk by the screening process actually do have the disorder in question. Diagnostic tests are usually complex and may have side effects. They should be able to discriminate definitively between those who do have the disorder and those who do not.

Some tests, such as ultrasonography, can perform both a screening and a diagnostic function. The boundaries between screening and diagnosis may, in some instances, become blurred and some would debate whether performing amniocentesis on all pregnant women over the age of 35 constitutes screening or diagnosis. In other instances, a diagnostic test may be applied where no

[1] References p. 45.

screening has taken place, as for example in the case of amniocentesis in families already including a Down's syndrome child (although even here, 'family history' could be interpreted as a primary screen).

The four tests can be summarised as follows:[2]

- *amniocentesis:* a procedure, usually performed at around 17 weeks of pregnancy, in which a small quantity of the amniotic fluid surrounding the fetus is withdrawn through a needle inserted through the abdomen and uterine wall. (Ultrasonography may be used to guide the instrument used to withdraw the fluid, but is not here the primary test.) The fluid and the fetal cells it contains may be tested for different disorders in the fetus.
- *chorionic villus sampling (CVS)*: a procedure by which a small quantity of the chorionic villi on the surface of the placenta is withdrawn for DNA analysis. CVS can be performed at any stage of pregnancy from about 8 weeks of gestation.
- *maternal serum alpha-fetoprotein (MS-AFP) screening:* AFP is a protein derived from the fetus, present in the amniotic fluid and also circulating in traces in the maternal bloodstream. The concentration of AFP in maternal blood serum can be used to screen for neural tube defects in the fetus and, it has been claimed more recently, for Down's syndrome too.
- *ultrasonography:* a process using high-frequency sound waves that can be focused and used to produce images of tissues, organs or structures within the body. Physical malformations can be detected with greater or less certainty depending on the quality of the equipment and skill of the operator. Repeated ultrasonography can detect fetal growth retardation. The timing of the tests is shown in Table 1.

Table 1 (adapted from ref. 2)
Fetal sampling process, timing and risks to pregnancy

Sampling process	Weeks gestation	Risks to pregnancy (%)
Amniocentesis	14–17	0.5 – 1
CVS	8+	2 – 4
MS-AFP testing	16–18	–
Ultrasonography	9+	+ *

* The risk is of false positive diagnosis leading to abortion of a healthy fetus.

2 THE DISORDERS

The conditions in question are Down's syndrome and neural tube defects (NTDs). New and dramatic advances have been made in the field of prenatal diagnosis through the introduction of DNA techniques which can now identify genetic diseases such as Duchenne's muscular dystrophy, cystic fibrosis, haemophilia, and Huntington's chorea. Although these new techniques are of considerable interest, this review focuses upon the four established tests named above.

Down's syndrome is the consequence of the most common chromosomal disorder: an extra element on chromosome 21 (hence its more formal name, trisomy 21), although other less common causes exist, namely translocation of genes and mosaicism. Down's syndrome is manifest in mental retardation, general growth retardation and lack of muscle tone. Important to this report is that its incidence increases with maternal age. (Higher paternal age may also be associated with increased incidence.) Overall, the incidence in the population varies between 1 in 600 and 1 in 1000 live births. Despite the increased risk of higher maternal age, the largest number of Down's children are now born to younger mothers, the main reason being the smaller number of women aged 35 and over who give birth. In Denmark, by 1985, only 3.6 per cent of Down's babies were born to women over 35 while in the UK 6–8 per cent of pregnancies occur in women 35 years and over, which account for 25–30 per cent of all autosomal trisomy fetuses. The overall 1-year survival for children born with Down's syndrome in Denmark in 1980–1985 was 85.4 per cent and the 6-year survival 73.7 per cent.

Neural tube defects (NTDs), one of the most common serious congenital malformations, result not from disorder of the genetic material but from a failure of the neural tube of the embryonic central nervous system to close. Neural tube defects are of three main types: spina bifida, anencephaly (these two occurring with approximately equal frequency) and encephalocele, which constitutes about 5 per cent of all NTDs. The incidence varies across EC countries (*Table 2*) – Northern European countries usually reporting a higher rate – and even *within* some countries, the incidence being higher in the northern or western part of the country.

The incidence also varies over time: within the UK (where records for this condition are good), birth incidence of anencephaly and spina bifida declined by 77 per cent from 3.15 to 0.62 per 1000 between 1964–72 and 1985.[3] Although part of this fall may be attributed to successful screening programmes, there must also be a natural decline in the condition.[4] The cause of the malformation is not understood, although environmental factors are important.

Women who have had either a Down's syndrome or NTD fetus already are at higher risk of having another affected fetus.

Table 2
Incidence rates (per 1000) of anencephaly and spina bifida in 19 European Registries of Congenital Anomalies and Twins (EUROCAT), 1980–86*

	Anencephaly (LB + FD + IA)		Spina bifida (LB + FD + IA)**	
Centre	No.	Rate	No.	Rate
West Flanders	19	.38	22	.44
Hainaut	32	.56	24	.42
Odense	12	.37	17	.52
Paris	88	.41	106	.49
Strasbourg	21	.32	45	.69
Marseille	14	.59	10	.42
West Berlin	15	.35	28	.65
Firenze	28	.44	35	.55
Umbria	10	.19	20	.38
Emilia Romagna	16	.12	61	.45
Dublin	225	1.37	313	1.91
Galway	18	.93	26	1.35
Luxembourg	3	.18	6	.36
Groningen	33	.66	32	.64
Glasgow	133	1.46	163	1.78
Liverpool	106	.87	162	1.32
Belfast	278	1.43	323	1.66
Zagreb	4	.21	8	.43
Malta	6	1.13	3	.56

* excluding cases associated with other dysraphic anomalies.
** LB, livebirths; FD, fetal deaths; IA, induced abortions.

Source: EUROCAT Working Group Report 3. Surveillance of Congenital Anomalies, 1980–86. Dept of Epidemiology, Catholic University of Louvain, Brussels, 1989.

3 THE DIFFUSION OF AMNIOCENTESIS

Chronologically, mid-trimester transabdominal amniocentesis was the first major prenatal diagnostic test to be used in many EC countries, and the acceptance or otherwise of this test laid the foundations for others to come. An early use of amniocentesis was to test for rhesus factor, but it became the main test for Down's syndrome, the amniotic fluid yielding the cells which were subsequently cultured (a process taking approximately two weeks) before the chromosomal analysis could be carried out. Today, if amniocentesis is performed at week 16 of pregnancy and karyotyping is required, the test will usually take at least 10–14 days. The test is highly accurate, and with skilled management is said to incur a small risk to the pregnancy.

Chromosomal investigations have been reported since the earlier part of the century, although it was only in 1956 that it was finally agreed that the number of human chromosomes was 46. At the time, considerable scientific interest was shown in methods of identification of fetal sex, in connection with prenatal diagnosis of sex-linked recessive disorders. Almost simultaneous publication of papers in 1956 on the identification of fetal sex through analysis of amniotic fluid cells indicated that experimental use of amniocentesis was being tested in Copenhagen, New York, Jerusalem and Minneapolis.[5] Three years later Lejeune and his colleagues advanced the science of genetics by identifying trisomic Down's syndrome through tissue culture,[6] while in 1960 Polani *et al.* identified the first case of Down's that was attributable to gene translocation.[7]

Fuchs, in Denmark, persisted with research on amniotic fluid and in 1963 succeeded in growing amniotic fluid cells in vitro. In 1966 and 1967 three American groups published results of chromosomal analyses performed on cultured amniotic fluid. The test was not highly accurate at first, but later achieved its high specificity and sensitivity.

The timing of events was significant in the diffusion of this new test. The late 1960s and early 1970s were, in Europe (and in the USA), a time of considerable social change. Political and social events led to a shift in public values and attitudes of greater tolerance to a wider spectrum of 'acceptable behaviours' (for example, homosexuality, and the abolition of capital punishment). An important, and in this case necessary, part of the social change was a 'liberalising' of the abortion law (*Table 3*), for it has been argued[9] that legalised abortion is *the* prerequisite to the development of prenatal diagnosis. However, because the changes in social values coincided with the advent of amniocentesis the impact of the one on the other is not always easy to identify (for example, in the UK). In some other countries (for example FRG, Sweden) abortion for specified medical reasons was already permitted.

Two countries have not conformed to this general trend in that abortion was and remains illegal. In Ireland abortion is illegal under any circumstances under the 1861 Offences Against the Person Act, and prenatal tests have therefore never been introduced officially. Where a fetus with a disorder has been identified (for example through the use of ultrasound, which in some centres is routinely used in pregnancy[10]), women receive counselling. In Ireland (as in other EC countries before the change in abortion law), women

Table 3
Date of liberalising of abortion law in EC countries and Sweden to allow termination of pregnancy

Country	Year
UK	1967
Denmark	1973
France	1975
FRG	1976
Greece	1977
Italy	1978
Netherlands	1984
Portugal	1984
Spain	1985
Belgium	1990
Sweden	1963

Source: Country reports (the revised legal conditions are, however, different in each country[8]).

have to travel to another country if they wish an abortion. It has been reported[11] that 'amniocentesis is available', and amniocentesis is apparently very occasionally carried out as a test for rhesus sensitisation. Unlike in some countries, however, the climate of opinion does not favour using amniocentesis for investigation only. Abortion in Ireland constitutes a felony, carrying with it a maximum sentence of life imprisonment, and doctors may be concerned that investigation of the fetus could lead to consumer pressure on members of the medical profession for action. We shall refer little more to Ireland in this report.

Northern Ireland should in theory be contained within discussion of the UK, but the 1967 Abortion Act does not extend to Northern Ireland and the latter's prenatal screening service, while well established, differs from that of mainland UK in some respects. Abortion on medical grounds is available, and the province performs amniocentesis, CVS and ultrasonography. Ambivalence over the abortion issue is perhaps indicated by the absence of routine MS–AFP screening, despite Northern Ireland's high incidence of NTDs (see Belfast figures, *Table 2*).

In Belgium, although abortion has until very recently been illegal, the situation is very different. Eight Centres for Human Genetics exist by Royal Decree (passed in 1987 and 1989), and the centres are State-funded. Belgian hospitals, and the seventeen family planning centres which form the 'Groupe d'Action des Centres Extra-Hospitaliers Pratiquant l'Avortement', openly practised abortion (voluntary abortion at the family planning centres and termination of pregnancy following the identification of abnormality at the hospitals). Although 'specialists in antenatal diagnosis stress the preventive nature of these tests to guide fetal therapy, to avoid unnecessary intervention and to plan medical care during childbirth and the newborn', the Belgian rapporteur also notes that most couples undergoing tests do realise that the discovery of fetal abnormalities implies the possibility of termination of the pregnancy.

Apart from the difficulties encountered in the diffusion of screening tests in countries where abortion is illegal, doctors and hospitals may also hinder the diffusion elsewhere, because of personal religious beliefs which preclude abortion. In Italy, for example, Caldwell notes[12] that doctors can opt out of doing abortions if they sign up as conscientious objectors: immediately after the passing of the abortion law in 1978, 72 per cent of Italian doctors signed up, the figure dropping to 59.1 per cent by 1983.

Amniocentesis was first introduced into Northern European countries at this time of social change (*Table 4*). The individual innovators, who often held an academic appointment at a university medical school, represented a number of disciplines: some were scientists, others medically qualified, for instance a physician like Polani in the UK or in the FRG an obstetrician, Knörr and his wife Knörr-Gärtner (a cytogeneticist), the couple joined later by a paediatrician trained in clinical genetics, Mürken.

Table 4
Date of introduction of amniocentesis into EC countries and Sweden

Country	Year
UK	1969
Denmark	1970
FRG	1970
Netherlands	1970
Spain	1970
Belgium	1972
Portugal	1972
France	1973
Italy	1975
Greece	1976
Sweden	1970–71

Source: Country reports

The German innovators, Knörr and Knörr-Gärtner, travelled to the USA in 1970 to attend one of the first international meetings on the benefits of amniocentesis. They knew, as did others, that the test would have to prove itself safe and that if they wished to set up even an experimental service using amniocentesis, they would have to build up the genetics service, since most EC countries ran only a very basic service. Laboratory services would have to be greatly improved in terms of staffing and resources, and obstetricians (or technicians) would have to receive a sound training in use of the technique. A genetic counselling service and an abortion service would also be required. Members of the medical profession and the general public would also have to be informed about the value of the test. All aspects of the introduction of the test would require more resources injected into the basic service.

One advantage of a small and cheap item of technology is that it provides freedom to innovate quickly without an initial requirement for major funding; it also avoids government controls and delays in purchasing which are more a

feature of large items of technology.[13] In the case of amniocentesis, several countries report that research money was initially used to finance its introduction (for example The Netherlands, Spain, Sweden and the UK). In Greece and Denmark, by contrast, Government money was used from the beginning.

Research funds could not, of course, be used to build up a genetic screening service. In order to incorporate this into the health service of the country, the innovators were required to make more formal representation of their plans to the Government. Thus a number of country reports note a similar process: in Sweden, FRG, Denmark, and France a group of doctors from various specialties drew up a blueprint of the genetics service of their country in terms of its administration, budget and laboratory capacity. Although costings and capacities have subsequently been revised, the original framework in each case still remains. In The Netherlands, an early report by the Health Council played a similar role. It is notable that several of the 'product champions' who initiated the service at this time continued to play a dominating, and sometimes constraining, role in its subsequent development.

In some EC countries, early use was experimental, confined to pregnancies which would in any case be terminated. In others (for example Spain, Portugal, Italy) amniocentesis was at first simply investigative, for abortion was not legal and no action could be taken even if a disabled fetus was identified. This remains the case in some hospitals, and with some practitioners, notably in Italy and Portugal.

Interestingly, amniocentesis was not at this stage subjected to proper evaluation of the kind subsequently attempted with CVS. Studies of fetal loss later quoted were often derived from three non-randomised studies carried out in the UK, in the USA and in Canada, published between 1978 and 1981, although other countries also studied risk (for example, The Netherlands). The only randomised controlled trial of amniocentesis was a Danish study in 1986,[14] derived from 4606 women aged between 25 and 34, which gave a 1 per cent risk of inducing a spontaneous abortion. Thus when amniocentesis was first introduced, each country calculated its own level of risk from the 'objective' risk of the procedure and the relative skill of the physician. When acceptably low rates were achieved, its application was extended to include low-risk pregnancies. The introduction of ultrasound in the early 1970s to help avoid puncturing the placenta led to an improved risk rate. Once the level of risk was thought to be low, and obstetricians had gained experience in its usage, the future of amniocentesis was at least temporarily secured.

The innovators who wished to establish this new test set to work to educate professionals and public. Publications describing the laboratory services and the test appeared in professional journals, and amniocentesis became a topic for research meetings and conferences. The Swedish report (*p 69*) gives a graphic account of the work of a small group of specialists in clinical genetics in 'selling' prenatal screening tests.

The case of the FRG presents an extreme example of this process of deliberate education, for a history of eugenic movements and 'mercy killings' of severely retarded infants had made the notion of genetic diagnosis highly charged. The successful introduction of a genetic screening service (and the adjacent discussion of legalised abortion) was successful because it was

skilfully planned. Amniocentesis was introduced into FRG in 1970. At the time, the genetics service had few resources in terms of laboratories, and only a handful of scientists and trained laboratory staff to carry out the cytogenetic and biochemical analyses. The innovators faced the task not only of convincing their colleagues and the public about the value of the tests, but also the need to lobby for considerable funding to build up the service. Because of the subject's strong negative connotations the innovators set up a 'high profile' meeting with press coverage in which to raise the broader issues and to present the test in a favourable light to both professionals and public. The first scientific meeting on 'genetic diagnosis in pregnancy' was held in November 1970 and the proceedings were published. After the meeting, public education about prenatal diagnosis continued, and like the Swedish innovators, the German pioneers knew the important channels for successful diffusion. The promoters of the new techniques held lectures for lay audiences, and made broadcasts and television programmes. New textbooks were developed in collaboration with the schools. When the German Genetics Society held their annual meeting in 1972 a public roundtable discussion on medical, legal and ethical aspects of genetics was set up and some of the most prominent scientific journalists in the FRG were invited to participate.

The effort was successful, for in 1972 the innovators proposed and received a multi-million DM grant from the German Research Foundation to set up a collaborative 7-year study on prenatal diagnosis of genetic defects. This priority programme essentially established the genetics service in FRG.

During the early period of diffusion the number of amniocenteses rose dramatically. Between 1974 and 1978, 5647 amniocenteses were performed in the FRG (population 61 million), 1900 in France (population 53 million) and 3027 in Denmark (whose population is only 5 million). Diffusion varied from a rapid and organised increase in usage in some countries to others where diffusion appeared considerably less controlled. The German and French genetics services grew in an apparently controlled manner, whereas in Italy the service is reported to have developed in a 'wildly uncontrolled fashion', with recourse to private funds to set up centres and laboratories besides relying upon the National Health Service to start genetics centres.

Diffusion in Spain was even more rapid. The law relating to abortion was changed in 1985; by 1988 29 centres were able to perform amniocentesis (23 of these centres also do ultrasound detection of malformations, ten centres CVS, and two DNA analysis).

The test is now available in all but one EC country. Reasons for the initial rapid diffusion are not hard to find. Amniocentesis opened up the potential for wholesale prenatal diagnosis on high- and low-risk women. The technique is relatively easy to learn and versatile, and the laboratory analysis is highly accurate. The social conditions, too, help account for its appeal to women. Amniocentesis appeared in Europe at a time when the birthrate was dropping or had dropped. In the UK and Denmark, the birthrate levelled off at just over one child per family, while in Portugal social changes led to a sharp decline in the birth rate, most strikingly in 1987–88 with a 20 per cent drop in family size. The ability to test for the 'normality' of the fetus appealed to couples who wanted their one child to be perfect. As a special case, in Greece,

one Athens hospital started a service of simultaneous fetal blood sampling and amniocentesis, to test for thalassaemia (a heritable blood disorder common in Mediterranean countries) as well as for Down's syndrome.

While the introduction of amniocentesis into EC countries is doubtless a success story, diffusion did not extend to saturation, ie the situation in which the test is used by all women potentially at risk. In FRG, the number of tests has continued to rise (see *Table 5*), while Danish figures show a classic diffusion curve with the number of tests levelling off. In Sweden too there is now mention of a levelling off. In none of these countries is there notable change in the birthrates. In Belgium, where the restrictive situation hindered diffusion, raw numbers have risen (see *Table 6*), although the scale of the increase is obviously much smaller.

Table 5
FRG: Number of amniocenteses by year

Year	No.
1971–73	193
1974	308
1975	893
1976	1,798
1978	3,925
1982	15,838
1984	22,506
1985	26,130
1986	31,180
1987	33,535

Source: Country report

Table 6
Belgium: Number of amniocenteses by year in one pioneering centre

Year	No.
1972–74	104
1975	34
1976	62
1987	667
1988	755

Source: Country report

What is noted in all country reports (and masked by total national figures) is regional variation within countries. Some variation is, not doubt, 'natural', but what is implied in the variation noted is a more complicated equation of variability in availability and accessibility of the test: see, for example, figures from Denmark (*Table 7*).

Table 7
Denmark: No. and rate of amniotic fluid tests by woman's county of residence, 1987

City/County	No. of births	Pregnant women undergoing amniocentesis	
		No.	%
City of Copenhagen	4907	597	12.2
City of Frederiksberg	802	106	13.2
County of Copenhagen	6273	804	12.8
County of:			
Frederiksberg	3510	469	13.4
Roskilde	2252	220	9.8
Western Zealand	3017	223	7.4
Storstrom	2508	210	8.4
Bornholm	535	37	6.9
Funen	4830	356	2.7
Southern Jutland	2909	311	10.7
Ribe	2658	226	8.5
Vejle	3698	425	11.5
Ringkobing	3297	304	9.2
Aarhus	6750	648	9.6
Viborg	2821	287	10.2
Northern Jutland	5445	535	9.8
Total	56221	5758	10.2%

Source: Danish data

The rapporteurs, particularly those from France, Greece and Spain, highlighted a 'capital city phenomenon', with uptake of amniocentesis much higher in and around Paris, Athens and Madrid. In Greece, for example, although the 25- to 55-year-old population in the Athens and Piraeus area is only 31 per cent of the Greek population, over 63 per cent of the referred cases come from the greater Athens area. Capital cities, of course, invariably possess a greater concentration of the country's population as well as more than their share of universities, teaching hospitals and research units and laboratories (an honour sometimes shared with a second city such as Frederiksberg or Rotterdam). In these cities professional and public awareness and knowledge of the test is higher; for professionals, geographical proximity to laboratories and to other professionals (through, for example, regular professional meetings) is important. For the women, access to doctors is usually easier, and 'capital city' women tend to be more highly educated.

Besides the special situation of capital cities, regional variation in uptake of amniocentesis is notable – in every country in the study, with the exception of Luxembourg. The latter is a special case: there are no genetics centres, but a group of specialists from a genetics department of the University of Liège (Belgium) come to Luxembourg each month to give genetic advice, and amniotic samples are sent either to Belgium or to FRG for analysis. Elsewhere,

however, considerable variations have been noted. In the UK in 1984, for example, the number of prenatal chromosomal analyses ranged between 20 and 45 per 1000 live and stillbirths in different Regional Health Authorities (England and Wales). The country reports from the UK and Italy indicate little direct relationship between the size of a region's population, the number of consultant clinical geneticists and the number of cytogenetics laboratories.

One explanation is geographical: in rural areas transport is poor, and islands and mountains form natural barriers. This may partly explain the slower diffusion of knowledge of the tests in Greece or Sweden within professional circles (through reduced opportunity for professional contact, local research meetings, and so on). In a single area of Sweden the ratio of the number of investigations to the number of pregnancies could vary from 0.87 for the area closest to the laboratory to 0.29 for a more distant one. Likewise, women's access to the medical services may be more difficult in such areas. The Italian example indicates this: while 25 of the 35 NHS centres are situated in the north of Italy, only seven are central and there are only three on islands; there are none in the mainland South. Women living in under-served areas wanting the test would either have to find a private centre, send samples to a laboratory or travel north.

But if geography could explain all, one would expect countries such as Belgium and The Netherlands to be a model of high utilisation. In Belgium, it is noted that the eight genetics centres are evenly distributed across the country, and that no financial barriers exist. Yet a 1986 study reported that upper and middle class women made greater use of the services. Similar evidence is presented from a Dutch thesis which records that in 1978, uptake by women aged 38 or over varied between 7 and 60 per cent in fifteen cities, with no relationship to the distance to the nearest centre. The author of the thesis, Thomassen, argued that the capacity of the laboratories was not a problem, distance was not an issue, no significant urban/rural differences existed and religion was not a deciding factor in uptake.

A significant factor mentioned by Thomassen and elsewhere is *attitudes* – the least tangible factor in the diffusion process, but a key one. Professional and consumer attitudes towards abortion and knowledge about the test are both vital to its successful diffusion. Since in most countries women have to be referred for testing the role, attitudes and knowledge of the test on the part of the gynaecologist or general practitioner is crucial. In France and the UK, doctors' attitudes towards abortion and screening have been the focus of research.[15,16,17]

In some Catholic countries (Belgium, Portugal, Italy), the views of some physicians on abortion account for a lack of referrals to genetic screening centres, and a block to the diffusion process. Other explanations point to poor (or no) genetics education at medical school, and consequently not just a lack of interest in such tests, but a more basic lack of knowledge about indications of genetic problems. Age can be a factor, as the rapporteur in Greece illustrates – young obstetricians being well informed and active in keeping up to date, but older ones continuing to practise privately in traditional fashion, it being more difficult to change their attitude. The Swedish and Greek rapporteurs have therefore suggested a combination of difficult geography and the

attitudes of some doctors as a joint explanation.

Utilisation of a service must depend upon the interrelated factors of physicians' knowledge and attitudes and those of their clients, although studies have more often focused upon *consumers'* behaviour. Research has indicated a clear relationship between uptake of amniocentesis and the social and economic standing of the women. The case of Greece illustrates this point, where one study at the University of Athens showed that in 25 per cent of couples requesting amniocentesis one of the partners had a university degree, which is true of only 10 per cent of all Greek couples. While one might be tempted to ascribe this pattern wholly to the existence of an extensive private health system which is more accessible to a middle-class Greek clientèle, the same phenomenon has been noted elsewhere. The report from the FRG (with its comprehensive health insurance system) documents a study carried out in Münster in 1983–5, where 76.7 per cent of the women undergoing amniocentesis were middle and upper middle class, and living in an urban or suburban area. It was also found that more of the women had themselves decided to undergo amniocentesis, whereas for women with less education the physician was more influential in taking the decision.

A French study carried out in the late 1980s led the authors to comment[18] that in spite of progress in diffusion, important socio-cultural differences remained between the pregnant women who obtain access to prenatal diagnosis and those who do not. The study, of a representative sample of women from the Bouches du Rhône area, indicated that the level of education was higher among the group of women (38 years and over) gaining access to

Table 8

Comparison of level of education between women obtaining prenatal diagnosis (1987) and the general population of pregnant women (Bouches du Rhône area, 1986)

	A level or university degree %	Secondary school only %	Primary school only %		*P*
‹35yr:					
Prenatal diagnosis (n=52)	46.2	19.2	34.6	)	
General population (n=2792)	29.1	24.3	46.6	)	‹0.05
35–37yr:					
Prenatal diagnosis (n=72)	66.7	27.8	5.5	)	
General population (n=151)	32.5	34.0	33.5	)	‹0.0001
›38yr:					
Prenatal diagnosis (n=112)	47.3	34.8	17.9	)	
General population (n=128)	30.4	13.3	56.3	)	‹0.001
Total:					
Prenatal diagnosis (n=236)	53.0	29.2	17.8		
General population (n=3071)	28.9	23.8	47.3		

Source: Moatti J-P et al.[18]

amniocentesis than in the general population of pregnant women, while for women under 38 years of age who had to contribute towards the cost of the test, the percentage with higher education was even higher (Table 8). Occupational status of the women gaining access was also significantly higher.

The French study and other related evidence should not be used to impute blame to certain consumers for not taking up the service offered; rather, it should point to a lack of accessibility of the service to less well-educated and less well-off clients.

The government, via funding for the service, likewise influences the extent and speed of the diffusion. It is difficult to weigh up the effect of different health care systems on uptake and usage of the test. Within the risk categories, genetic screening tests are available to women free in all countries, either through a national health service or through social insurance, or occasionally private health care, particularly in Greece or Italy. (In Italy, the point is made that within the NHS the service is free, but space is limited, while within the private sector the service is not free but there is laboratory capacity.) While it has been suggested that the fee-for-service system encourages more testing (one example here would be the case of France and ultrasonography) and thus would increase uptake, perhaps more telling is that *despite* the disparate systems of funding, all countries report an uneven distribution of the test. Of course, this finding is true for procedures and tests other than those in prenatal screening.

At governmental level, arguments using economic and cost/benefit analyses are, on the whole, seen as an unacceptable basis on which to discuss decisions about funding the genetic screening service – although there are important exceptions where an economic argument has been influential.[19] In Sweden, the notion of applying an economic argument to the broad field of prenatal diagnosis raised considerable debate, with representatives from societies for the handicapped arguing (successfully) that an appeal to economics was not a legitimate way to plan a service. However, although it may not always be acceptable to refer explicitly to economic analyses, economic thinking does lie behind many of the decisions made about the genetics service. At a crude level, one can see that government support of the service as indicated by the number of genetics centres is not necessarily related to 'need'. Thus in rural Greece, Southern Italy, and some parts of Spain, there are very few centres where diagnosis can be carried out.

Once the centres have been set up, there are other ways in which governments can affect diffusion, by restricting expansion of service. Thus resources may not increase in proportion to the rise in demand, the number of tests performed, or broadening of the range of tests. Laboratory services are very vulnerable to fluctuation in budget allocation, and in at least three countries (Greece, Spain, and especially Portugal) they have been reported to be insufficient to cope with demand in the very near future.

Other devices, too, can restrict the service provided. In the UK, France, The Netherlands, FRG and possibly elsewhere, amniocentesis was first made available to women identified as at risk by a wide range of genetic indications (such as being the parental carrier of a balanced chromosomal aberration or

having had a previous child with a chromosomal aberration) and advanced maternal age, as well as to women who came into the category 'maternal anxiety'. As the years have gone by, changes in risk criteria have appeared. Recent data indicate that laboratory capacity is largely taken up by the testing of older women – the cut-off age varying between 35 and 38, see Table 9.

Table 9
Percentage of laboratory capacity taken up by amniocentesis for older women

Country	Percentage laboratory capacity
Belgium	65 per cent for women 35 years or more (1973–83)
Denmark	91 per cent for women over 35 years (1986)
FRG	80 per cent for women 35 years of more
France	87.9 per cent for women aged 38 and over
Sweden	75 per cent for women over 35 years

Source: Country reports

There is no evidence that the variations in lower age limit are due to differences in prevalence of the condition. Rather, access to testing in a country (or region) is the result, it seems, of indirect budgetary control. The UK rapporteur notes that as hospital budgets have been cut, the age limit for eligibility for amniocentesis has risen. Guy's Hospital is said to have increased its age limit for amniocentesis from 35 to 36 a few years ago because of a lack of resources, and then reverted to 35 years, albeit without publicising the change, when extra resources were provided by South East Thames Region.

Related evidence comes from France, where discussion took place about whether to reduce the age barrier of 38 following demand from women aged 35–37. The French rapporteur has argued that dropping to the age limit of 35 would lead to laboratory activity being overstretched, and the proposed change was not justified by the modest benefit in identification of Down syndrome fetuses in the lower age group. An alternative hypothesis[18] suggests a stronger element of professional control in the decision, a point to which we return in the final chapter of this review. In Spain, despite increasingly successful attempts to inform older women about the risks of Down syndrome, the number undergoing chromosomal analysis remains very small: about 12 per cent of all pregnant women are older than 35, but of them only 5–7 per cent undergo amniocentesis or CVS. Other countries' data likewise show that not all older mothers under amniocentesis – in FRG the figure is about 50 per cent, in France nearly 60 per cent (1988), whereas in Belgium in 1983, only about one-third of pregnant women over 40 underwent the procedure.

Unofficially, it is said in a number of countries that the age criterion is breached in cases where a younger woman is exceptionally anxious, or has medical contacts. Maternal anxiety, as a reason for amniocentesis, is perhaps the category most susceptible to cutbacks. In Italy, the rapporteur notes that the younger age groups and maternal anxiety are represented in the new

services only where capacity is not yet saturated (overall, about 5 per cent are done for that reason). In a Swedish report of 1981, maternal anxiety as an indication varied from 30 per cent in some counties to virtually none in others; by 1985 about 10 per cent of cases were for reason of maternal anxiety. In FRG 8.2 per cent of amniocenteses are performed for this reason; its rapporteur suggests, however, that as a category it will always exist 'as long as prenatal diagnosis is not granted to all pregnant women who wish to obtain it regardless of their risk' (personal communication).

An uneven distribution of facilities, techniques and tests is encouraged by a decentralised system of health service funding. In Sweden, UK, Denmark, Italy and FRG funds are allocated to 'regions', 'counties' or 'states' where the decisions on how to spend them are taken. This system allows the development of a particular service where there are reasonable funds and where there is an enthusiast who has a certain degree of influence of political 'weight'. Where no enthusiast exists, or where competition for funds is strong, the service may be considerably less well developed (or for some prenatal screening, non-existent).

In many EC countries amniocentesis has never been given an official 'stamp of approval' via a central programme or positive funding, but has been left to develop without a strategy. Several rapporteurs have argued (and this may be more broadly true) that the government has consciously refrained from any official policy on prenatal screening and diagnosis. One reason suggested in The Netherlands, FRG and UK is the unspoken link with abortion. Governments may be unwilling to appear to condone abortion by support of prenatal diagnosis. As the Swedish report notes, the difficult ethical problems associated with prenatal diagnosis may have made politicians and administrators avoid taking a clear stand on a controversial issue.

In summary, we have described a number of factors which have served to hinder the diffusion of amniocentesis, but the information available is insufficient to distinguish their relative significance. They are: that the amniocentesis centres themselves are spread across countries in a way which is not directly related to 'need'; that geography cannot be ignored; that the attitudes of the local referring doctors are important; that the woman's mobility and class may be influential; that governments seldom engage in direct influence of a genetic screening service but that governmental methods may indirectly restrict resources for running or expanding the service; and finally, that the mechanisms of health service funding may leave development of services to politics at local level.

4 CHORIONIC VILLUS SAMPLING

For a decade or more, some EC countries practised amniocentesis followed by chromosomal analysis, to the satisfaction of many. The test is reliable, versatile and safe to use. A major drawback, however, which emerges particularly in the psychosocial literature[20], is that of mid-trimester abortion. Yet until the early 1980s, attempts to procure fetal genetic material for analysis in the first trimester had proved unsuccessful.

An early record of first-trimester sampling stems from Denmark where in 1968, two Danish doctors, Hahneman and Mohr, undertook chromosomal investigations on placental biopsies. Lacking real-time ultrasound, they carried out the procedure under direct vision using a special fibre-optic hysteroscope. The study was abandoned after a high rate of miscarriage and too little growth in the cell culture. CVS was started in China in about 1970[21] and the results were published in a Chinese medical journal. The villi had been aspirated 'blind' (ie without the use of ultrasound), and fetal sexing had been carried out directly by examination for Barr bodies, tissue culture not being available. The rate of pregnancy loss, considering the method, was not high, but CVS was discontinued because of the high demand for fetal sexing and subsequent abortion of fetuses of the 'wrong' sex (although CVS is said[22] to have been revived recently for genetic diagnosis).

Attempts at CVS in Sweden (1973), the USA (1979) and the Soviet Union (1982) all testify to the desirability of first trimester sampling, as well as to its difficulty. These early attempts foundered for various reasons. The trans-cervical instrument had to be large enough to contain fibreoptics to locate the chorion. The difficulty of 'seeing' the villi meant that incorrect material was sometimes aspirated, and the test had to be repeated – which could lead to complications such as infection and miscarriage.

In the early 1980s, Ward and his colleagues at University College Hospital (UCH), London, were searching for a means of early diagnoses for their patients. The group specialised in the treatment of women from Asian and Mediterranean origin, who have a high risk of carrying the genetic disorder beta-thalassaemia. Aware that mid-trimester abortion was particularly unsatisfactory for women from these cultures, the group developed a technique for transcervical withdrawal of chorionic villi, using a prototype fine (1.5mm) flexible cannula (subsequently manufactured by 'Portex'). In discussing with their patients the possibility of first trimester CVS, the group quickly came under pressure to use the technique for prenatal diagnosis. By this time ultrasound could offer a higher resolution picture of the location of the villi, thereby allowing the procedure to be performed without fibreoptics. The addition of a microscope at the bedside gave greater accuracy to check that villi had been withdrawn. These developments decreased the risks which had hitherto been the main problem.[22] Three un-anaesthetised women successfully underwent CVS at UCH in mid-1982.[23] A number of professionals from other centres susbequently visited UCH to observe the new technique. Yet the women had been high-risk, and for CVS to have widespread use, it would have to match the safety record of amniocentesis.

Early publications on prenatal diagnosis by CVS evinced considerable

optimism as the benefits of CVS were spelled out.[24] Although CVS requires more skill to perform than amniocentesis, it offers several advantages. There is no necessity for cell culture, and the consequent rapid processing time (1–2 days) allows the mother to make a decision about termination within the first trimester. Other benefits stem from this: women have less time to worry about the result, and if an abortion is appropriate, it can be carried out before the woman has become obviously pregnant. Abortion can be performed by vacuum suction, preferable to both the woman and hospital staff. The main potential drawbacks are the possible risks, which are more difficult to estimate during a period of fetal development in which spontaneous losses are more common. The first publication from the Canadian trial on this point is promising[25], whereas a 1990 study in Holland[26] recommends waiting, for women over 36, until 12 weeks, when the rate of spontaneous abortion after CVS compares favourably with the natural miscarriage rate.

Italians were among those who showed considerable interest in CVS. They took the technique back to Milan and introduced it in large clinics. Testing of the 'Portex' cannula on both a high- and low-risk population extended its possibilities. The development of CVS is sometimes attributed to the Italians because, the Italian rapporteur argues, the *cytogenetic* technique was developed by Simoni in Milan. Testing was initially confined to Milan in 1983–4, because other Italian clinicians were unable to obtain the Portex model. Subsequently, the diffusion of CVS was rapid.

Interest from other EC countries was also growing, although not all operators opted for the transcervical method and the original 'Portex' cannula. Danish doctors who had pioneered a transabdominal technique on pregnant women who wanted a legal abortion began to experiment with the transcervical method too. On the basis of the success of both techniques, CVS was offered by 1983 to pregnant women as an alternative to amniocentesis in both the Aalborg department (transabdominal) and the Copenhagen department (transcervical).

Because innovators were able to introduce the test into an already existing genetics service, there was little time lag between countries (*Table 10*); within countries, too, statistics indicate that CVS was adopted at a rapid rate.

Table 10
Date of introduction of CVS into selected EC countries and Sweden

Year	Countries
1982	UK, France
1983	Belgium, Greece, Italy, Spain, Denmark
1984	FRG, Netherlands, Portugal, Spain

Source: Country reports

Professionals and consumers were by the 1980s more knowledgeable about the potential of genetic screening and diagnostic tests, although reports suggest that within some countries the demand did place additional strain on the existing laboratory services.

Data from Denmark also suggest that CVS is unevenly diffused across the counties, and this is no doubt true elsewhere. Through their initial link with the Italian innovators, German geneticists started using the transcervical method (and although both methods are available, the transcervical method still dominates). Swedish clinicians started to perform CVS by the transcervical method in Lund in 1984 (although not using the 'Portex' cannula) and in Stockholm in 1985, but in 1986 the transabdominal method, pioneered in Denmark, was begun in Uppsala and Lund. Within a short time, the innovators had convinced the Swedes that it was a superior method, with a much lower miscarriage rate (figures quoted were 1.6 per cent for transabdominal, 11.9 per cent for transcervical). Swedish practice has shifted to the use of the transabdominal method, and with increased ratio of CVS to amniocentesis (*Table 11*).

Table 11
Use of prenatal diagnosis methods in Sweden, 1972–88

Year	Amniotic fluid	CVS	Deliveries (1000)	% >35 years
1972	90	–	112	6.9
1975	627	–	104	6.9
1979	2810	–	96	7.1
1980	3499	–	97	8.5
1985	4161	181	98	11.7
1987	4854	258	105	11.4
1988	5245	434	112	11.8

Source: Country report

France took a slightly different route. There, researchers attempted CVS with the use of biopsy forceps, but found this to be rather unsuccessful, with a high miscarriage rate. The French subsequently changed to the transcervical method. No single enthusiast appeared to 'push' the test, and reservations about the test from geneticists prevailed, the arguments presented in the French report being that being that the risks were not known and were probably higher than for amniocentesis. Further, there were reservations over the cytogenetic analysis. In one study in 1984, out of 25 French cytogenetic laboratories studied, only five had begun to carry out CVS. CVS *is* available in France, but hesitancy about the test remains. Usage is restricted to certain centres, mainly in Paris and Strasbourg, and elsewhere in special circumstances.

An existing link between the World Health Organisation (WHO) and University College Hospital, London, established through the work with haemoglobinopathies, led to a WHO-organised meeting in 1983 (and subsequent Report[24]) of the then experts in CVS to discuss its future. It was decided that rather than follow the same pattern of unevaluated introduction of amniocentesis, an attempt should be made to assess the value of

CVS and coordinate its introduction centrally. As a consequence the WHO International Registry of CVS was established in Philadelphia under the direction of Laird Jackson, the principal aim being to monitor the growth of CVS. This registry still operates, although its purpose has been superseded now that the technology has become, at some level, 'standard'. Jackson himself writes 'When the registry reaches over 60,000 it seems like you're just adding up more numbers. . .' (personal communication).

The other major issue debated at the meeting was the evaluation of the safety of the procedure by randomised controlled trials. Two separate issues were at stake: the respective merits of the transcervical and transabdominal methods of entry into the body, and the relative risks and benefits of CVS over amniocentesis. It was intended that the protocols of trials conducted in different countries would be (as they in fact are) mutually compatible, so that results could later be amalgamated. While a well-executed study might have answered the critics of the technology, in fact the situation was not so well controlled.

A trial funded by the British Medical Research Council was set up in 1985 with proposed widespread involvement from EC and other countries; in actual fact, to quote Durand (the project leader) 'the responsibility for evaluating CVS through a randomised trial falls on some of the northern countries where amniocentesis is already well established. . .'[27] Thus the trial gained collaborators from Denmark, Italy, The Netherlands and the UK, but a number of other countries did not take part, simply allowing the technology to develop. The Italian rapporteur reports on the fluctuating commitment of the Italian geneticists to the trial; in 1986 'five centres with the largest CVS practice agreed to join a randomised study. Six months later, only three centres were still recruiting in the trial, one alone having randomised more than 50 per cent of the cases.' However, 'in 1987 members of the trial decided, because of doubts raised about CVS, to join the British MRC trial in order to obtain as quickly as possible a definition of the risks involved in each method.'

In other countries, because of lack of agreement between the centres practising CVS, some doctors set up a service offering the test without joining the trial. Some argued that 'fetal diagnosis in the first trimester cannot ethically be withheld from any woman who presents early enough in pregnancy to take advantage of it'[28]. German doctors were explicitly opposed to a randomised clinical trial and instead sought and received funds in 1985 to carry out a 5-year collaborative study to assess CVS, with more than 27 university centres participating. The belief that the merits of the test outweigh other concerns was one reason for the pressure to diffuse the test without proper evaluation; another important influence was summed up by the Danish rapporteur (and others), who noted the test's attractiveness to women: 'there is a feeling among the doctors involved that the women who are randomised to amniocentesis are disappointed', a sentiment foreseen in the WHO report of 1983.

But the story of the diffusion of CVS is unfinished, for although the test did diffuse rapidly by 1986 there were indications of concern.[29] The WHO trial and early publications had focused upon the possible risks of the technique

early in pregnancy, but what emerged subsequently was a rather different problem. The potential misuse of CVS for fetal sexing which led to its cessation in China is reported as an issue of concern by a number of countries (Sweden, FRG, Denmark, UK). Other technical difficulties were now also being raised. The Italian rapporteur comments:

> 'By 1987 the general enthusiasm for CVS had been smothered by unanticipated technical problems; mosaicisms were being diagnosed in 1–1.5 per cent of cases, which – though often confined to the placenta – nevertheless needed exclusion by amniocentesis, and worse still, Simoni had reported two false-negative diagnoses resulting in the birth of severely affected children, and a few more had been published elsewhere. Half of the services started using both the direct and the culture techniques, thereby losing the technical advantage over amniocentesis.'

Concern existed, then, over discrepancies between the chorionic villi and the fetal karyotypes recorded. To guard against this possibility, some laboratories (in parts of the UK, in Italy, Denmark, and possibly elsewhere) initiated the practice of backing up results from the direct method with analysis after cell culture, a practice which is reported to be continuing. This does not negate the value of CVS but places a query over its superiority as a test over amniocentesis. Furthermore CVS, like other first-trimester tests, requires that the woman has early contact with the health service, a precondition that might not be easy to fulfil with some women, eg those living in poorly served rural areas (where there is already evidence that they undergo fewer amniocenteses) and also in EC countries where prenatal care is not hospital-orientated, such as The Netherlands.

However, there is no doubt that the *principle* of first trimester genetic testing has been accepted by professionals and consumers across the EC, and pressure continues to find safe and reliable means of first-trimester testing. From Italy, FRG and the UK, including Northern Ireland (and from the USA) there are reports of first-trimester amniocentesis testing. Although the method is experimental, it appears that the culture of fetal cells is possible at 12 weeks and, some would suggest, even earlier. Some geneticists have argued that they would prefer to continue to work with amniocentesis, that they are familiar with this test and that it is reliable. While the rapporteurs from Belgium and Sweden have suggested that eventually CVS and other techniques may eventually supersede amniocentesis, it is difficult to predict now, in 1990, whether the problems with CVS may be overcome, or whether CVS may simply have heralded a new era for amniocentesis.

5 MATERNAL SERUM ALPHA-FETOPROTEIN SAMPLING

MS-AFP is a screening test carried out between weeks 16 and 18 of pregnancy to check for the presence of a neural tube defect (NTD) in the fetus. The procedure stems from the finding that a higher than normal AFP level in maternal blood, due to leakage of AFP from the fetus, is an indication of open neural tube defect. The distribution of AFP concentrations in pregnancies with a fetal NTD overlaps with that in unaffected pregnancies, so that the test is not unequivocal or diagnostic; a positive MS-AFP test is followed by other tests, initially ultrasonography to check (by measurement of fetal length) that the presumed gestational age is correct and to exclude alternative explanations of high AFP values such as twin pregnancies and threatened miscarriage. The test has a sensitivity of about 80 per cent for open spina bifida and 90–95 per cent for anencephaly.

If a high AFP level is detected, diagnosis is usually reached by amniocentesis followed by measurement of AFP concentration in the amniotic fluid, with an additional test for acetylcholinesterase (AChE) as a secondary measure, or high-resolution ultrasonography of the fetal cranium and spine. If the result of any or all of these is positive, termination of the pregnancy is offered. MS-AFP testing, then, is a screening test, the first of a series of checks for abnormality.

The test was initially introduced on its own, later with date of conception checked using ultrasonography. With improved technology and skills, however, it has become possible to identify anencephaly and with more difficulty spina bifida, using high-resolution ultrasonography. This development has increased dependence upon ultrasonography to the stage where most would now agree that 'ultrasound examination is an integral part of the screening programme'[30]. Indeed, ultrasonography is so valuable as a test that in some countries (eg France) and in some regions of the countries that use MS-AFP, ultrasonography forms the primary screening test (see Chapter 6 on Ultrasonography).

This chapter is concerned with MS-AFP testing as a *screening* test, that is, a test used on a total population as a means of identifying those who might be at risk and would require further investigations. AFP also appears in amniotic fluid, but AFP measurement in amniotic fluid is a *diagnostic* test, performed after an amniocentesis. Because of the low incidence of the condition in their country, the reports from Belgium, Greece, Italy and Spain have commented simply that there is no national screening programme for neural tube defects based on MS-AFP; instead, AFP concentrations in amniotic fluid are measured if the mother is thought to be at high risk. In the FRG and parts of the UK, AFP and AChE determinations are carried out routinely after all amniocenteses.

The pattern of diffusion of MS-AFP testing in EC countries is very different from those for amniocentesis and CVS. The reports present rather chequered histories of its introduction and diffusion within a country, reflecting uncertainty over whether the test should have widespread application as a screening test. In Denmark, FRG, The Netherlands and Sweden, routine screening of the population is currently available only in certain areas. In the UK, whereas there is a national screening policy, MS-AFP screening is not available to all women in every region there.

AFP was first characterised as a fetal product in 1956, but at that time the possibility of screening was not realised. Interest in the potential for MS-AFP screening occurred later, in the early 1970s. In 1972 the first report of a higher than normal MS-AFP in an anencephalic pregnancy from Japan was noted, the same year that Brock (a medical geneticist who originally trained as an organic chemist) published papers in *The Lancet* on the use of amniotic fluid AFP measurement in prenatal diagnosis of open spina bifida and anencephaly.[31,32] Further papers were published in 1973 noting the link between a large proportion of the cases and MS-AFP and according to one commentator, 'it was immediately realised that maternal serum measurements might be useful as a screening test for open neural tube defects'. Screening started on an experimental basis in the UK in 1974, and in 1975 a 19-centre UK Collaborative Study was mounted to establish standards and to determine cut-off points which would indicate the need for diagnostic investigation via amniocentesis.

MS-AFP testing was enthusiastically introduced into Denmark, FRG, The Netherlands and Sweden, all in 1974, although always on a regional basis, and in each case through a collaborative study which was necessary to establish the 'normal' levels of MS-AFP at each gestational age in that country. The pattern of diffusion then becomes less clear-cut. No national screening programmes have been mounted, despite evidence that some professionals agreed to an expansion of the service. In at least two countries working parties will report on this issue in the near future.

In the UK the Collaborative Study was coordinated by Wald, an epidemiologist, who had previously been concerned with other research using maternal serum, and who had read about Brock's work on AFP. To finance the statistical and computing back-up that such a large study would demand, funding was sought from disparate sources; in the end, the study was paid for in part by the centres involved in the research, in part by money from disparate sources – a research foundation (The Wellcome Trust), a civil engineering firm, a drug company, and two small charities. The study was chaired by the established figure of Polani, from Guy's Hospital, London. The study group set the upper cut-off levels for the UK, and subsequently went on to publish scientific findings on amniotic AFP, the risk of amniocentesis and the role of acetylcholinesterase as a secondary diagnostic test for NTDs. The work was regarded as authoritative by the medical establishment and published from 1977 onwards.[33]

After the initial publication, dissemination within the UK was rapid: of 98 Area Health Authorities, 31 were undertaking MS-AFP screening routinely by 1977, and by 1979 another 14 had been added, giving a 46 per cent provision of screening in the Areas by the end of the decade. A Department of Health draft circular was then published which encouraged the idea of routine screening during antenatal care throughout the country. Much professional opinion was, at the time, against the idea, as the UK rapporteur notes:

> 'A definitive circular was never published, because of adverse criticism especially from the Royal College of Obstetrics and Gynaecology. They felt that the costing estimates were unrealistic and that the whole concept was based upon the unjustified assumption that adequate

ultrasound facilities and expertise in their use were available throughout the country. A College reply to MP Keith Hampson also registered the profession's objection to political pressure being applied to influence clinical judgement.'

Instead, a professional working group was set up, chaired by Sir Douglas Black. It was later reported that most doctors were in favour of a national screening service; however, the working party did not unequivocally recommend this, but instead produced guidance on factors to be considered by each health authority in deciding whether to offer it.[34] One reason which militated against a country-wide screening programme was the marked variation in incidence of the condition within the UK – Wales, Scotland and Ireland have much higher and the east side of the country much lower rates. The Scottish Home and Health Department also established a working party, chaired by Professor James Walker, which came out in full support of screening opportunities for all expectant mothers. In Northern Ireland, where incidence is also high, no routine screening programme has been set up, MS-AFP being carried out only on an individual basis. Ambivalent attitudes within the province over abortion are considered a deterrent.

In 1978 an evaluative project was set up to study the optimal operation of a service, and South Wales was chosen as the study area. The report of this study[35] concluded that an overall efficacy rate of 65 per cent for the detection of spina bifida was realistic, and outlined three unrelated problems which together combined to reduce the over-all effectiveness of the screening:

a) a significant number of women attended the antenatal clinic too late for testing, for a variety of administrative and other reasons);
b) the use of ultrasonography was not (at the time) sufficiently expert;
c) some obstetricians were avoiding amniocentesis indicated by a high MS-AFP, preferring to trust a negative ultrasound finding rather than risk aborting a normal fetus.

No new central funds became available, and provision has continued to be, as with amniocentesis, on a variable regional basis, with those locally interested arguing for – or against – a regional screening programme. A study carried out for the Maternity Alliance in 1982 identified the considerable variation which existed in England and Wales, with five Districts offering ultrasonography as the primary screening test rather than MS-AFP. A review of the service in 1985 by Cuckle *et al.*[3] (*Table 12*) underlined the lack of a national programme and monitoring system, and emphasised the ability of an individual to influence local policy.

Debate continues over the relative merits of MS-AFP and ultrasonography as the primary screening test, with some regions relying on the latter; it may be that in regions with lower incidence of the condition the cost/benefit ratio works in favour of the apparently more expensive technique of ultrasound screening.

In other EC countries MS-AFP testing also started in the early 1970s. In Sweden the test was instituted after the first reports appeared in international journals. There was a prime innovator, Dr B Kjessler, and the drug company which made kits offered financial support to the subsequent projects to study

Table 12
Maternal serum AFP screening rate in Regional Health Authorities in England and Wales (1985)

Region	Women tested	Mid-trimester pregnancies	Screening rate (%)
	(a)	(b)	(a/b)
Oxford	35423	33600	105
North East Thames	52284	52800	99
Trent	57315	59600	96
Mersey	24635	33400	74
North Western	39805	56400	71
Wessex	21987	35500	62
South East Thames	26269	47600	55
Wales	19537	37300	52
West Midlands	33331	71400	47
South West Thames	17208	36900	47
North West Thames	21730	48200	45
South Western	15469	38100	41
Yorkshire	19459	48700	40
Northern	11474	41500	28
East Anglia	912	24900	4
Total	399288	666200	60

Source: Cuckle *et al.*[3]

the test. As in UK, the first objective of the innovator was to set Swedish standards, and a large-scale study was proposed. Between 1975 and 1980 MS-AFP screening was evaluated in two large clinical projects. The findings of the first study, which reported in 1977 on 7158 cases, indicated technical problems and a second study was mounted, with continued enthusiasm from medical professionals. This study aimed at a population of almost 23,000 women, 80 per cent of whom agreed to participate. In 10 per cent of the cases the test had to be repeated at least once and in 0.9 per cent amniocentesis was performed. The detection rate improved in this study, and 16 out of 21 cases were diagnosed during the second trimester, 14 of whom were terminated with legal abortion. AChE was brought in as a secondary test.

By 1980 approximately 20 per cent of all Swedish pregnancies were tested for neural tube defects. This rate dropped, however, to less than 10 per cent of pregnant women being offered MS-AFP screening in 1985, and by 1988 only three areas of Sweden offered it. Several reasons emerge for the decrease in use of MS-AFP screening. The Swedish rapporteur notes as the main reason the low specificity of the test, which resulted in a heavy workload for the doctors and much-disliked anxiety of the women receiving false-positive results. MS-AFP appears to have triggered a national debate, conducted

through the media, about the benefits and drawbacks of screening, in which the MS-AFP screening programme was especially criticised. The debate is referred to in Chapter 7.

MS-AFP testing is performed in Belgium on all women whose pregnancies are monitored in the nine university hospitals.

Although FRG, Denmark and the Netherlands all mounted pioneering screening projects in selected regions of the country in the 1970s, none of the countries has instituted a national programme of screening, despite evidence that such a programme could be successfully operated, and arguments that it would be cost-effective.

In FRG between 1979 and 1982 more than 50,000 pregnancies were screened in a collaborative study, but despite the obvious feasibility of the programme it was not implemented; in contrast to Sweden, there was apparently little debate on the topic.

About 20 per cent of the Danish total pregnant population was being screened by 1980. From 1980 to 1983 an 8-centre study, financed initially out of research funds, sampled the sera of 70,000 pregnancies. The conclusion from this and subsequent studies was that MS-AFP should gradually be extended to the whole country, providing that good follow-up facilities and equipment, primarily good quality ultrasonography, were available. The possibility of running a national programme of MS-AFP testing in Denmark had been under discussion at various levels since 1981. Denmark's Health Board has never stated conclusively that a national programme should be mounted. The most recent situation is that a working party was set up in 1986 to examine the economic consequences of making the service available nationally. As Denmark uses both MS-AFP and ultrasonography to screen for NTDs, the optimal mix of the two tests is to be decided by another working group set up by the Health Board.

The Netherlands introduced the test in 1974, with two regions running routine MS-AFP screening projects from Groningen and Utrecht. In other parts of the country parents who were at risk (ie who already had had an affected pregnancy) had access to amniotic fluid AFP testing, with an 80 per cent uptake. There were no further major developments until 1987, when the Health Council in The Netherlands, a semi-independent government-funded body, decided to propose a screening programme using MS-AFP for all Dutch pregnant women. Referring to the two regional projects, where there had been good co-operation from women, a participation rate of 80 per cent and identification of 67 per cent affected fetuses were aimed for. The proposal set out the disadvantages and advantages of the screening programme, including the cost-benefits. The draft proposal did not receive the consent of the chairman, who pointed out that the same arguments could suggest that such a service was *not* in the best interests of professionals and the public. This move by the chairman, himself influential in setting up clinical genetics in the Netherlands, stymied the report for some time. A new chairman was appointed and a second compromise report was drafted, which proposed that routine screening should operate in one-fifth of the country as a pilot scheme. As yet, the Health Council is awaiting the government's response.

Given the early introduction and apparent acceptance of the test in the

1970s in a number of EC countries, one may ask why MS-AFP testing is not now routine in those countries? Several factors may have hindered its successful diffusion: those relating to the nature of the condition and those relating to the test.

Neural tube defects are little understood. The prevalence varies between and within countries. Moreover, while there appears to be a widespread decline in the incidence of the disease, it is also not known whether this may not rise again in the future,[4] and to what extent the decline may be attributed to successful screening.[3] Improved maternal nutrition and possibly other environmental factors are believed to play a part. These uncertainties make future planning for a national screening programme difficult – for it is pointless to dismantle a service which may be required in the future, yet inefficient to continue to resource the prevention of a naturally declining condition beyond a certain minimum level.

Thus the 'stalling' of any national screening programme and the maintenance of regional routine screening may be seen as a way of dealing with an uncertain situation. Some areas with higher incidence have apparently better services, so that screening *is* routine for certain regions in EC countries, for example, in the west of Scotland in the UK.

Decisions about national screening are also affected by the test itself. MS-AFP values vary with gestational age and certain conditions, for example a multiple pregnancy or threatened miscarriage, and are also said to vary by race, weight and diabetic status of the mother. The interpretation of test results is not always easy, especially as the national and regional cut-off points appear to be changing (falling) over the last few decades. Setting cut-off points is difficult, as they relate to both the condition and the test.

Brock himself correctly identified the weakness of the test: 'The major point of attack on MS-AFP testing comes from its lack of specificity'.[36] With low specificity there will be a number of false positive results which lead to a considerable number of subsequent investigations to exclude the possibility of disorder. The results of two Swedish studies (1977–1980), while not necessarily typical of other screening programmes, illustrate the problems which may be encountered and which are said to have contributed to the decline in enthusiasm for routine application of the test in Sweden. Findings from 23,000 pregnant women revealed eight cases of raised MS-AFP *and* amniotic fluid AFP which subsequently yielded three legally aborted apparently normal fetuses, four normal infants born and one spontaneous abortion.

Doctors in all countries were also concerned about the social and ethical problems raised in allowing spina bifida babies 'through the net' (with false negative results). Both the German and the Dutch rapporteurs voiced concern that such incidents could damage the good reputation that the genetic services had built up, while additional testing of women with false positive results would induce considerable maternal anxiety. Some negative feedback from the media substantiated those fears, while consumer groups indicated some ambivalence over screening and NTDs. From The Netherlands come reports that while the Association for Spina Bifida and patients favour screening, the orthodox Protestant media stress the right to life of spina bifida children, and loss of healthy fetuses. Danish concerns have been voiced on the

same topic.

To set up a good MS-AFP service requires good facilities in terms of good quality ultrasound equipment, counselling and diagnostic services. A national screening programme would therefore require a high level of such facilities across the country. Concern over the quality of back-up were voiced in the UK in the early 1980s and has been noted elsewhere (eg in Denmark), although high-resolution ultrasonography is more likely to be generally available in main centres today.

Within the general question about screening for neural tube defects lies a second debate over technology, namely whether to use MS-AFP or ultrasonography as the primary screening test. Routine MS-AFP screening does not exist in France. Here, as in certain areas of other countries, ultrasonography predominates. The incidence of NTDs is a little higher in the West of France, especially Brittany, but the French report notes that since half the anomalies are anencephalies, ultrasonography is considered satisfactory as the main test. MS-AFP testing is used in Brittany. In a study of 23,000 pregnancies in Rennes, where MS-AFP testing was available (free) at the doctor's request, 16 spina bifida babies were identified, some of those through ultrasonography. In Finistère, the preference remains for good quality ultrasonography, although certain categories of women have access to MS-AFP testing if the doctor thinks it necessary. The French are also trying out primary prevention through the administration of folic acid and multivitamins to women who have previously had an affected fetus.[37]

What is the future of MS-AFP screening? At the same time that the possibility of a national programme of routine MS-AFP testing was being considered in The Netherlands and in Denmark, a UK article was published[38] (following an American lead on the topic) arguing that a *low* AFP level could be seen as a significant indicator of Down's syndrome. A Danish study subsequently confirmed the findings. The article, which showed that maternal age, MS-AFP testing, and a combined assay of HCG and oestriol could be used as a method of screening for Down's syndrome in young women, could lead to routine *screening* for Down's, aimed at reducing the number of Down's babies born to younger mothers.

Screening for low AFP levels has now started. In FRG, analysis for low AFP started in some centres in 1986. In the first year, 282 analyses were reported. In the UK the combined test has been used on a population in England and Wales, and since July 1987, in the West of Scotland. In this latter area, where routine MS-AFP screening of 80 per cent of pregnant women has been conducted for some years, such a shift in policy was relatively easy to make. It is predicted that diagnostic testing (eg by amniocentesis) will in future be based on risk factors rather than maternal age alone, as a result of information gained from the new assay.

For MS-AFP testing to become a major screening test for Down's syndrome has important implications for the genetics service of all EC countries. None at present has routine MS-AFP testing in all regions, and all have, as we have already seen, committed considerable laboratory space to testing older women by chromosomal analysis of amniotic fluid. Routine screening of all pregnant women would result in a change of population

undergoing amniocentesis, with fewer older women and more young women included. New contacts would have to be formed with practitioners, who would have to be educated about the implications of the tests. In the past, in countries with a less intrusive approach during pregnancy (Sweden and particularly The Netherlands), doctors have opposed the introduction of a routine screening programme, Dutch doctors pointing to the organisation of maternity care in The Netherlands with its higher percentage of women who may not experience hospital-based prenatal care. Will these arguments be overturned by the new test? At present these debates – over laboratory space, the potential (and for some, the questionable) value of the combined assay, and fear of litigation by older mothers – mean that it is difficult to predict whether there will be a new lease of life for MS-AFP testing. As a test for NTDs, however, MS-AFP testing is unlikely to be completely replaced by ultrasonography, for many cities across the EC simply do not have the high-quality equipment or staff with which to detect the abnormalities.

6 ULTRASONOGRAPHY

Of the four tests in this report, by far the least information was provided for ultrasonography in almost all country reports; one interpretation of this is that unlike the other tests, the diffusion of ultrasound investigation has been so extensive and unregulated, the technology now so successfully embedded into everyday obstetric practice, that the rapporteurs somehow found it difficult to study. Conversely, the early developmental stages of obstetric ultrasonography have been documented in some detail by Yoxen[39], Oakley[40], and others. Local studies of ultrasonography are reported by some country rapporteurs.

The foundations of ultrasonography were laid in 1917 in the field of naval warfare. The potential for clinical application emerged in the 1920s and 1930s, and in 1942 two Austrian brothers named Dustik made the first claim that ultrasonography could be used diagnostically. Yoxen's 1987 account indicates the slow refinement of the technology, with innovators exploring the parts of the body and tissues on which sonar scanning worked best. By the 1950s ultrasonography had been tested in a number of medical fields, extending to cardiology, ophthalmology and physical medicine.

Use of ultrasonography for obstetric purposes was pioneered by the professor of midwifery at Glasgow (I Donald). Working with a junior colleague and in conjunction with an engineering firm, Donald published the first paper[41] on the use of obstetric ultrasonography in the differential diagnoses of pelvic masses. Yoxen notes the financial investment from industry at this time, suggesting that even then it was thought that the yield would be high. Despite this pioneering work obstetric ultrasonography had a slow start. It was five years before others began to publish confirmation of the work. Thereafter the use of ultrasonography as a diagnostic technique in obstetrics gradually grew in Europe and the USA so that by 1988 it was said[40] that modern obstetrics and gynaecology could not be practised without it.

The technical problem that faced the product developers was to make the image sharp enough to be clinically useful. The first ultrasound images were static and difficult to interpret and ultrasound could be used only for crude diagnoses. By the early 1980s real-time ultrasonography had been introduced, providing a moving picture of the fetus which, over the years, has continued to improve in resolution so that today it has an increasing role in the direct diagnosis of NTDs, severe skeletal dysplasias and abnormalities of the abdominal organs. Ferguson-Smith suggests[30] that at least some of the diffusion of obstetric ultrasonography in the 1970s could be attributed to the introduction of MS-AFP screening which 'helped to improve the obstetric services generally by encouraging the widespread introduction of obstetric ultrasound'; certainly, while ultrasonography is an integral component of the procedures in amniocentesis, CVS and other forms of prenatal diagnosis (for example, fetoscopy), it enters the debate more centrally in the detection of NTDs.

However, high-quality ultrasound scanning requires good equipment and skilled technical staff to diagnose structural abnormalities. Although details are not given in the EC reports, it is unlikely that all countries have access to state-of-the-art, and therefore expensive, technology. In the

UK, one topic of concern in the early 1980s with the MS-AFP programme was the then lack of availability of high-quality equipment and staff across the country. It is likely, then, that much of the reported use of ultrasonography is not for diagnostic, but for screening purposes, where basic ultrasound scanners are adequate for the identification of gestational age and multiple pregnancies and, later, to assess fetal development.

While the country reports lack detail on ultrasonography, they do indicate its widespread (and sometimes repeated) usage as a screening test in pregnancy. Ultrasonography was introduced into Denmark in 1964, with equipment invented and developed by three Danish doctors. In 1969 the first ultrasonography laboratory was established on the initiative of these innovators, attached to a department of obstetrics and gynaecology in Copenhagen. In 1972 ultrasound scanning was first used in Denmark as an aid to amniocentesis and there, as elsewhere, became an essential part of the procedure. The diffusion of ultrasonography is indicated by a 1982 study which showed that about 80,000 ultrasound investigations were carried out by 29 departments. A 1985 study showed that out of a sample of 3023 pregnant women, 70 per cent had had at least one ultrasound examination without amniocentesis, and of that number, 50 per cent had had one scan, 26 per cent two, 9 per cent three and 14 per cent four scans or more. In 1984 the Danish Society for Obstetrics and Gynaecology recommended that ultrasonography should be used nationally early in pregnancy. After assessing the situation, however, the Health Board's Medical Technology Committee recommended in 1986 that on the basis of the then existing evidence that there were not grounds for routine screening in pregnancy. The Danish rapporteur notes that many experts in the field did not agree with this, and in fact, ultrasonography continues to be offered routinely to pregnant women. By autumn 1988 ten departments routinely screened women once in pregnancy. The conflict of opinion over the use of ultrasonography for routine screening in Denmark is evident elsewhere, with ambivalent opinions expressed in both professional and lay press.

In Malmö, where Swedish ultrasonography expertise was developed, all women received (1975) two ultrasound scans during pregnancy – one at week 17–19, and the other at week 33. The Swedish rapporteur reports slow diffusion of ultrasonography across Sweden during 1975–80, but by 1980 all university departments of obstetrics and gynaecology had access to the technology and in three of them it was used for routine examinations in early pregnancy. Despite the failure of the Swedish MRC to recommend routine screening, the number of Swedish women undergoing screening appears to be rising, and a recent estimate suggests that 80–85 per cent of women receive one scan, with further scans if required. Figures from other EC countries confirm the widespread incorporation of ultrasound scanning as a screening test in pregnancy. A recent study in Westfalia (FRG) reported that 83.9 per cent of all pregnant women received one scan before 21 weeks. Even in countries where the overall budget for prenatal services is small, such as Portugal, the rapporteur records that practically every pregnant woman receives one scan. Likewise in Greece, Trakis notes (personal communication) that in another EC study 'it seems that almost all women have at least one ultrasound examination during pregnancy, and these are women who attend

public maternity clinics, ie they are in the lower economic strata – one can imagine what happens in the private clinics. We even observe gypsies waiting in the corridor for ultrasound'.

It is, however, the French doctors, possibly more than in any other EC country, who have embraced ultrasonography. From 1972 to 1981 the number of women receiving ultrasound scans increased from 9.8 per cent to 81.8 per cent. The figure has now risen to 96.1 per cent. The Consensus Conference on obstetric ultrasound in 1987 recommended that only two routine scans should be made for low-risk women. However, one French study reports that 65.8 per cent of a representative sample of the population of pregnant women in South-West France[42] receive more than two ultrasound scans per pregnancy, while figures for Lille women stand at six! Some are performed for screening purposes, for as chapter 5 indicates, the French rely on ultrasound for the detection of structural abnormalities. One 1988 study[43] made in the Bouches du Rhône area showed an overall sensitivity of ultrasonography for the detection of major fetal anomalies of 75 per cent; 87 per cent of anencephalies were detected prenatally during the second trimester through ultrasound scanning, but only 22 per cent of spina bifidas (which, of course, more frequently survive). The study reflects some concern about the lateness of some diagnoses, as well as the effectiveness of the technique.

One explanation offered for the reliance on ultrasonography is that the combination of a fee-per-test for ultrasonography for the obstetrician, plus women's (or couples') pleasure at being able to see the fetus, means that both medical professionals and consumers are equally enthusiastic about the technology (Leloup, Aymé, personal communications). It could be argued that the purpose and timing of each scan should be known if one is to estimate the economic impact, but the considerably greater use of the technology in France than in some other EC countries suggests another, more cultural explanation. Payer notes that in the past, the French were also enthusiastic about X-rays, and the author suggests[44] a cultural desire to 'see' the diagnosis.

Little dissension appears to exist over the use of ultrasonography for diagnostic purposes. But as with other tests, ultrasonography has not been strictly evaluated (for a summary of the evaluative studies see [45]), and both in the country reports and elsewhere there is evidence of some professional concern over the possible hazards of ultrasonography as a *routine* screening test. A *Lancet* editorial sets the tone of concern regarding its apparently limitless diffusion: 'Increasing knowledge provided by ultrasound coupled with its simplicity and apparent safety have led to its early and possibly premature spread into clinical practice'.[46] In the mid- to late 1980s expert conferences were held in EC countries to consider its safety and use in routine screening (eg in France and the UK[47]) as well as the USA.[48]

There is little indication that the routine use of ultrasonography will diminish in the near future. Considerable resources have been invested by industry in the development of real-time scanning, and the technology is continually being refined. And while certain consumer organisations may raise the safety issue[49] there is no doubt that the possibility of seeing the fetus from the 11th or 12th week onwards is for many a positive experience, and one that many consumers would not wish to be withdrawn.

7 THE ROLE OF PROFESSIONALS, GOVERNMENT, CONSUMERS AND THE MEDIA IN THE DIFFUSION PROCESS

Professionals

The key persons in the diffusion of prenatal screening tests are members of the medical profession who, two decades ago, were not necessarily medical geneticists but often from other medical disciplines (for example, paediatrics or obstetrics). When amniocentesis was in its early stages of diffusion, these doctors were usually obliged to set up a medical genetics service, to argue for resources to staff and run laboratories, and to persuade their medical colleagues of the advantages of the test.

The establishment of medical genetics as a specialty within medicine and the introduction of genetics into the medical curriculum was also often pioneered by these innovators. Another important part of their role has been to liaise with the media and the public, and this review has already noted instances of successful promotion in FRG and Sweden. A number of the country reports suggest that the innovators have remained influential in organising and directing the prenatal service – and while their enthusiasm and perseverance with the tests may well have been influential in promoting the tests, their role may also become one of control; they have become the gatekeepers of the discipline. One example of this comes from the FRG, where many of the same scientists concerned with making amniocentesis available later became involved with the introduction of CVS; they were apparently opposed to a randomised controlled trial, and instead proposed and received a 15 million DM grant for a collaborative study to assess the merits of CVS.

Doctors, like other professionals, may adopt an innovation for a variety of reasons. Some are spurred on for career reasons (since medical advancement is often built upon research initiative) or because of the other benefits of the research activity. From the Spanish report comes open recognition of this: 'The role of professionals in the development of prenatal diagnosis has been of special importance, on some occasions because of its scientific interest or because it was a way of obtaining financial resources for their laboratories.' An observer of the field writing about the debate between CVS and early amniocentesis comments that in one country 'there seemed to be a split between those who started off in CVS and had made a splash and those who weren't included in the original diffusion and were turning towards 'early amniocentesis' to strike back. The ploy of the early amniocentesis contingent is to claim that amniocentesis, as every wise fool knows, is a perfectly safe procedure because, after all, it is just amniocentesis. . . That the possible dangers of early amniocentesis might be investigated is simply a hindrance in the way of marching ahead and striking back at your competition. So goes the path of scientific research.'

In countries where private practice exists, the profit motive must enter if consumer demand has been stimulated. In these situations, being ahead of the field, being an innovator, may simply be seen as a way of attracting more clients to one's practice (or hospital) than one's competitor. In other reports

(and in discussion with those involved in the field) a more charitable motive emerges, and there is no doubt that the belief that a particular technique is useful, and a desire to diminish the suffering associated with genetic disorders, has pushed forward the boundaries in the field.

Whatever the motives for becoming involved with the prenatal screening, doctors are the key actors in the diffusion. They retain considerable control over health service spending at the local level in each country and, despite direct public access to the tests in some countries through private health care, doctors remain the main route of referral to the tests. Their attitudes towards certain tests, their preferences for certain styles of practice, are vital to the diffusion process. These attitudes can either help or hinder the speed at which a test may be taken up. It has been argued that attitudes vary by age and – more difficult to illustrate – the closeness of links with other innovators and hence receptivity to new ideas.

Perhaps the most basic intra-professional division in this field is religion, which divides doctors, notably in Catholic countries, over the issue of abortion and the related issue of the desirability of prenatal screening tests. In some countries (Italy, Portugal, Spain) access to the service may be limited by the number of doctors – and hospitals – willing to do these tests. The Portuguese report spells out the options available to a woman requesting information and screening from general practitioners and obstetricians. They face one of three responses: doctors do not agree with prenatal diagnosis because the eventual outcome may be abortion, and refuse to collaborate; or doctors accept prenatal diagnosis, inform their patients and send them to the appropriate centres, but do not commit themselves to the possibility of termination; or doctors fully inform their patients, take part in the samples and commit themselves to the end.

The Portuguese report notes that while the Association of Catholic Doctors were against prenatal diagnosis if it necessarily led to termination, other doctors were in favour of giving all available information (from tests) to their patients; this was true also in Spain. Thus although the Church is a significant influence, some doctors use as their main reference group their broader professional body. One cannot assume, then, that a country with a large number of Catholic doctors will necessarily have little prenatal testing, and interestingly, popular opinion may also favour its development: 'Important groups of opinion favour the idea that Catholic physicians and even confessional hospitals should assist couples interested in being informed about the status of the fetus' (Spanish report). There is less evidence of influence from the Protestant Church, although in Sweden an ecumenical group of experts published a 1980 report 'Fetus, Family and Society' which was influential in the national debate.

The ambivalent views of some doctors hindered the implementation of national MS-AFP screening policies – not on religious grounds, but along moral/ethical/professional lines. Despite arguments that the service would be cost-effective, doctors in Denmark, The Netherlands and Sweden voiced reservations about the test, citing as reasons against it the necessity to introduce additional back-up tests and the considerable patient anxiety that false positive results would bring. On the whole, doctors appeared to use the

normal channels of professional communication in blocking diffusion, for example, arguing in professional journals, at conferences and so on against the introduction of a test; however, it is also clear from undocumented evidence that some diffusion was blocked by innovators in the field, who used their status as senior statesmen to influence decisions. This was especially true in countries where health care is centrally funded.

State control over the introduction and diffusion of prenatal screening tests seems less strong than for the other innovations in this EC project. In Ireland and Northern Ireland, strict regulation is enforced and use of the tests is minimal. Elsewhere, regulatory mechanisms vary. There has been little control over the diffusion of ultrasonography and its use is widespread, whereas with the other techniques discussed here stricter professional and Governmental controls are in evidence. However, several rapporteurs underlined the lack of proper evaluation of amniocentesis when it was introduced. The Swedish rapporteur notes that wide experimental use of the test creates demand for it, thereby making subsequent evaluation more difficult to set up. Although she illustrates this with the case of MS-AFP testing, the same process bedevilled the attempted evaluation of CVS, and as we have seen the trials were conducted only with difficulty.

Control is partially managed through the creation of a restricted number of centres for analyses, although (most notably in Greece, Portugal and Italy) private centres exist about which little is known and for which no data are available. Government regulations in most countries give details of the number of approved centres – for example, 39 permitted in France in 1988; eight in Belgium, three in Greece and so on. In some countries there is regulation over allotted tasks: thus The Netherlands has seven centres, analysis for metabolic diseases being almost entirely performed in Rotterdam, four centres designated to do DNA analysis and three for prenatal cytogenetics studies (although the tasks may eventually be carried out in all laboratories). Funding obviously restricts the number of centres, but it is also argued that the restriction is concerned with quality control. The French report suggests a strictly controlled growth of the genetics service, giving the reason for the poor availability of amniocentesis, which is restricted to women aged 38 or over, as one of costs and benefits, with quality control implied. Others have queried this, pointing to the unchecked use of ultrasonography in France.[18]

One concern is laboratory workload: if this is too small, standards drop; if too high, pressure is created to set up another laboratory. In countries where the service could expand considerably but where funds are not forthcoming, the strains are considerable; for this reason it is difficult to predict the future development of prenatal diagnosis in Portugal.

One attempted way of controlling quality (in the absence of legal controls) is through the creation of professional groups to monitor developments in the field and to provide mutual support and education. Most countries report some form of professional association. Private laboratories have sprung up in Italy and the issue of quality control is highly topical: with few ethical committees in existence to oversee the field, there have been professional attempts to control activities, first through the setting up of a National Registry which required registration of genetic screening. The group eventually

formed the CESNA group, concerned with technical and ethical issues which arise in practice. The first two objectives of the group were 'to generate consensus on all prenatal diagnosis procedures currently in use, and to create an anthology of ethical problems encountered in everyday practice.'

The function of the *Spanish Association for Prenatal Diagnosis* is to represent its members internationally, to coordinate experts and to liaise with the public. The Association publishes a quarterly Bulletin, with information on its activities, meetings and congresses and a bibliography on prenatal diagnosis topics.

Government

In all countries members of the medical profession have been represented on Government committees influencing the funding and nature of the genetics service. The long-term acceptance of the original framework in a number of countries is either a tribute to their perceptiveness at the time, or else a comment on the difficulty of changing basic health service structures.

In all countries, the Government has played an indirect role in affecting the diffusion of prenatal screening tests through financial support (or otherwise) of the service. In some countries, support has increased as the service has expanded (eg Sweden, Denmark). In others, as already noted, lack of funds has restricted development of the service (Greece, Portugal). Despite the importance of funding, it has been noted that cost-benefit analysis is not the central pivot for decision-making about service provision. Whilst several rapporteurs document the influence of economic analyses on screening programmes (eg Denmark in 1977), economic arguments are often rejected (as in Sweden) as a reason for prenatal screening. Take, for instance, the Dutch report on MS-AFP testing:

> The cost-benefit ratio of AFP screening is positive. However, cost-effectiveness is only one factor in the decision-making. No one wants to be accused of preventing the birth of handicapped children only to please the budget, so the bright financial side of AFP screening is not a political advantage in all respects.

Apart from the obvious importance of Government via funding for prenatal screening, the other major reason for Government involvement in the field has been over ethical issues. Thus a number of occasions have brought a reluctant Government into the controversy because of society-wide ethical debates (eg surrogacy, in vitro fertilisation); production of reports at high level such as the 1988 Glover Report[50] will no doubt increase.

Several rapporteurs have noted an increasing Government, and indeed society-wide, awareness of the potential of genetic investigation. This is becoming increasingly complex, especially with the introduction of CVS and DNA techniques which can be applied not only to prenatal diagnosis but also to screening for carriers of the gene. Although in the past a Government may have had a 'wait and see' policy in which no comment or intervention was made unless necessary, the issue of abortion, to name one of the contentious

areas, may be felt to require legislative changes. With a shift in both the potential of reproductive technologies and improved neonatal care, a few rapporteurs have shown that discussion about abortion has resulted in questioning of the upper gestational age for legal abortion. Some groups (Sweden, Netherlands, FRG) are worried that high-level discussion of these issues will re-open the abortion debate itself, possibly to the detriment of those arguing for abortion on demand.

The abortion issue and others, of which fetal sexing is perhaps especially pertinent to this report, have appeared on Governments' agendas (eg in Sweden, FRG, Denmark, UK) – all countries in which Government and professionals wish to exercise control over the potential use of genetic technologies primarily for fetal sexing. In Denmark, an Ethical Council was finally created in 1987 as a result of debate in the media in which politicians, doctors and spokespersons from handicapped societies were represented. An agreement was made between the Ministry of the Interior and the Central Scientific-Ethical Committee of Denmark that information about fetal sex should be withheld from couples until the 13th week. In the FRG, thinking along similar lines by the professional organisation of medical geneticists led to the creation of an ethical board, and the decision to withhold this information until the 14th week of gestation.

Consumers and the Media

We have already seen, in examples from FRG and Sweden, that manipulation of the media is vital to the diffusion of a new technology. The media reporting of prenatal diagnosis in all countries has generally been low-key, the topic not being seen as newsworthy as 'expensive' medical technologies, eg organ transplants, despite the fact that small technologies such as prenatal screening tests are likely to affect a far greater proportion of the population than would many of the expensive technologies. Yet it was also noted by several rapporteurs that the media have been very positive in presenting prenatal screening tests as worthwhile.

News media form an important source of consumers' information about prenatal screening tests, and the positive reporting may well have contributed to the rapid diffusion of the tests (noted in a Dutch thesis, in Sweden and in Portugal). Media debate, of course, may simply increase public awareness of the tests without necessarily presenting them in a positive light: the Swedish experience of MS-AFP testing, where the rapporteur suggests that the general debate of 1978–9 probably prevented automatic inclusion of MS-AFP screening as a routine part of antenatal care, is the most obvious example of this. It is important to remember that in France, Italy, Spain, Portugal and Greece, society-wide debates through the media (TV, newspapers, radio, women's magazines) do not occur in the same way as in some of the Northern European countries.

Several of the rapporteurs presented information on consumer knowledge about prenatal screening. One study suggested that 50 per cent of Spanish women knew about the relationship between advancing maternal age and the increased risk of Down's syndrome. In a Lisbon hospital, in Portugal, a small

study was carried out on women attending for prenatal diagnosis. Of the sample of 85 women referred, 64 per cent were said to be 'not at all informed', and only 4.4 per cent were judged to have sufficient information about the test. By contrast, in Denmark, where amniocentesis had been available for longer, a Gallup (a media research institute) survey in 1983 showed in a representative sample of women that 95 per cent of women were familiar with the possibilities of that test, and 90 per cent in favour. In the UK it was noted that although screening developments had been confined to women's pages in the quality press, more recent developments (such as the ethical considerations raised previously) have moved the topic onto the national pages of the same papers.

The accessibility of the technology to women returns us to a discussion about religion. Several rapporteurs spelled out the view of the Catholic Church which in its orthodox form is against all forms of screening and voluntary interruption of pregnancy. But just as that influence varies amongst professionals, so too do consumers differ in the extent to which they might follow the Church's ruling. The Spanish report notes the role of some liberals in allowing women to undergo prenatal diagnosis, while the Portuguese study mentioned above adds that although 73.5 per cent of the sample said they were Catholics, 'they agreed unanimously that acceptance of prenatal diagnosis and abortion was not linked to religious beliefs'. While this sample may have been biased, it does reinforce what studies from elsewhere have argued (eg Thomassen from The Netherlands) that religion is not *necessarily* the key factor in abortion decisions following prenatal diagnosis.

Demand for the test from individual consumers has always been said to be high, although the influence of the consumer is often difficult to document, and in the country reports must be derived from anecdotal comments. Individual consumers have undoubtedly had some impact on the provision of the different tests. One obvious example in this review has been the rapid introduction of CVS which, in the absence of hard research, some rapporteurs have suggested indicates considerable consumer appeal. Overall, the ready acceptance by many consumers of the concept of prenatal diagnosis is a major factor in the success of these tests. The reports did describe some instances of pressure being placed on the consultant to carry out the test (eg France, FRG, Sweden, Portugal) – sometimes by women too young to satisfy the official criteria for testing, for example in France, where women in the 35–37 age group volunteered to pay for the test themselves. Some women have sued their doctor when they have not been offered the test and have given birth to a disabled child (eg UK, FRG, Sweden). One could argue that fear of litigation might play a more significant role in increasing the number of tests in the decades to come, as European health professionals more overtly adopt the American practice of defensive medicine.

The tests themselves are not without their problems for consumers, as a number of psychological and social studies have indicated. The rapporteurs from Sweden, Netherlands, Denmark and the UK have all made reference to studies assessing the acceptability of testing and the psychological repercussions. The growing literature in this field from EC countries (and the USA) has played a part in articulating consumer views and in documenting consumer

problems in relation to the 3 to 4 week wait that the culture of amniotic fluid requires.

One cannot assume that consumers have always been wholeheartedly in favour of prenatal screening. In several countries, the abortion debate re-opens every few years. Here, pro-life groups may be joined by organised groups of handicapped people who fear that social service provision for those born with handicap may be reduced if fewer handicapped children are born. Such organised groups have, in different countries, expressed diametrically opposite views on the overall issue of whether or not to screen. In The Netherlands, the positive influence of the group of handicapped people who 'strongly favoured' screening was in part offset by a small but well-organised orthodox Protestant media. In the FRG, a large donation from a German consumer foundation (Lebenshilfe) was Gnstrumental in setting up the first genetic counselling service in Munich. Such groups undoubtedly continue to educate the public about the longer-term problems associated with different handicaps; simultaneously, there is greater awareness of the positive lives that handicapped individuals can lead.

Several rapporteurs point out that less surgery is done today on spina bifida babies and the quality of life of these infants may have improved, while in the reports and elsewhere[51] the point has been strongly made that even with a good genetics service, only a small proportion of handicap is identified and averted. These issues are better aired through society-wide discussion in some countries (eg Denmark) than in others. Doctors' views are not homogeneous; depending on individual experience they may be for or against screening and diagnosis. In Sweden, for example, some doctors working with a group of handicapped people had adopted their values, arguing against screening.

Radical feminists across Europe and the USA have campaigned against acceptance of reproductive technologies, including prenatal screening. At the 1985 International Conference of FINNRAGE (Feminist International Network of Resistance to Reproductive and Genetic Engineering) women from a number of EC and other countries reported on the progress of reproductive technology in their country, noting also the activities of feminists and consumer groups.[11] Though much of the discussion is confined to the feminist literature, in the FRG both the 'Green Party' and feminist socialists are critical of reproductive technologies, and continue to demand closure of all prenatal genetic diagnostic and counselling centres, arguing not against abortion in general but against the abortion of affected fetuses. Militant feminist groups issued threats to the services as well as to those running them, and in Münster in 1985, Rota Zora, an underground organisation, planted a time-bomb which destroyed the genetic counselling centre at the medical school.

8 THE 'NORTH–SOUTH DIVIDE'

The reports from the 12 EC countries have documented the diffusion of not simply four separate tests, but essentially the rise of the genetic screening service as we know it today. Each of the tests has its own history, and earlier chapters identify at least some of the factors affecting the extent to which a test has been promoted in some countries and not in others.

A further general factor in the diffusion of genetic screening tests arises from a comparative consideration of the reports: a 'north–south' divide. Although the dates of the primary innovation are often very similar in different EC countries (for example, with CVS), we can see quite striking differences in the extent of the diffusion within each country thereafter. All countries except Ireland reveal some activity in the field, but the number of health service genetics centres performing analyses, and the crude number of tests carried out per head of population distinguish the countries' activities sharply. Table 13 is incomplete (no data for Italy, UK), but will serve to make the point. The tests referred to are chromosomal analyses consequent on amniocentesis and CVS.

Table 13
Country, population, genetic centres, number of chromosomal analyses after amniocentesis and/or CVS, by year

Year	Country	Population* (000s)	Centres	Centres/ Pop (m)	Chromosomal analyses**	Analyses/ Pop (000)
1987	Denmark	5124	4	.781	6791	1.325
1988	Sweden	8276	6	.725	5245	.634
1988	Belgium	9859	8	.811	4640	.471
1988	Netherlands	14220	7	.492	5200	.366
1986	FRG	61658	31	.503	33272	.540
1987	France	53788	39	.725	13783	.256
1988	Greece	9646	3	.311	1787	.185
1988	Portugal	9738	4	.411	200***	(.041)
1988	Spain	37458	29	.744	1139	.030

* OECD 1987.(population as of 1980.) ** *Source:* Country Reports.
*** in 2/4 centres (Oporto).

There are indications throughout the reports of reasons why it may be easier to innovate in some northern EC countries. A simple answer might be that this depends upon having the funds to do so. While the relative economic strength of the northern countries is certainly important, in this field religion and, more intangibly, the social climate also play a significant role.

To turn to the importance of financial backing first, funding was required both for the product champions to attend international conferences at which amniocentesis was discussed, and more importantly, for them to return to their countries and 'piggyback' the test on other research funds at their

hospitals. Even here, differences may exist across the EC, for some countries rely on wealthy Governmental and private research foundations, typically deriving from an earlier period of industrial and financial success. The role of industry as a source of back-up funding may be less crucial than with large-scale technologies, but is nevertheless apparent throughout the history of this diffusion.

A few examples should suffice. In FRG, a top-up grant of 500,000DM was donated by West German industry to help establish the priority programme; in the UK two firms contributed towards funding the influential AFP Collaborative Study; in Italy the rapporteur confirms that 'budgetary constraints to acquisition of equipment are generally quite easily overcome, either by contracting private providers or through donations or charge-free loans provided by the manufacturing industry'.

Countries who have come later to industrialisation may find it harder to turn for extra funding to industry or to research foundations for loans, donations and gifts and thus the north–south divide should perhaps more accurately (but clumsily) be named the 'early/late industrialising countries' divide. While one could argue that the overall amount donated from industrial/research foundation sources may be small, the reports suggest that in the absence of health service backing, the availability of private sources was initially crucial – and conversely, the lack of them is reflected in the underdeveloped nature of the services, eg in Greece and Portugal. Of course, both north and south countries benefit from the investment made by industry in the larger technologies such as ultrasonography, but of course the northern countries were more likely to have the funds to buy and update their equipment.

Another major reason for the north–south divide is of course that southern EC countries are most influenced by the Catholic church. Attitudes towards genetic screening are closely related to those on abortion, and these countries have to face more difficulties in setting up and running their genetics services because the basic rationale of a screening service flies in the face of the Church's rulings.

Less easy to document when discussing north–south differences is the social climate which influences factors such as receptivity to experimentation. Again, research funding plays a crucial part, but so too does a less easily defined attitude of questioning the status quo. The country reports are insufficiently detailed to explore this, but the importance of opportunities for a broad social exploration of certain issues (for example, ethical) are mentioned by the rapporteurs from Denmark, Netherlands, Sweden and the UK.

Further factors relevant to the diffusion process such as the background and professional links of the early product champions, details of the presentation in the media of the issues, and impact of consumers' attitudes to the tests, must await further study.

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HISTORY OF PRENATAL GENETIC DIAGNOSIS IN THE FEDERAL REPUBLIC OF GERMANY

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THE WEST GERMAN HEALTH CARE AND HEALTH INSURANCE SYSTEM

The Federal Republic of Germany (FRG) currently has a population of about 60 million. About 90 per cent of the population is covered by health insurance funds ('sickness funds') and about 8 per cent by private health insurance. The sickness funds are organised on the basis of geography (Ortskrankenkassen), occupation (Betriebskrankenkassen), trade (Innungskassen) and income. Depending on the member's economic status, he or she is either a voluntary member of a health insurance fund or must join on a mandatory basis. Included in the group of the compulsorily insured are almost all blue collar workers, and white collar workers with incomes below a certain level. Parallel to the compulsory insurance system, 'substitute funds' (Ersatzkassen) have developed, whose members are mostly white collar workers.

There are about 1500 autonomous health insurance funds. Although each fund is expected to be fiscally autonomous, its financial matters are supervised at the level of each Bundesland ('Land' or province). Overall supervision rests with the Federal Government's Ministry of Labour and Social Affairs. Since each sickness fund must operate within statutory guidelines which prescribe, among other things, the benefit package that must be offered the insured under Statutory Health Insurance, the funds are actually fairly similar to one another.[1]

The health insurance funds' over-all scheme provides full coverage for all medically necessary services, including ambulatory and in-patient care, prescribed drugs, medical appliances, dental care, etc.

Physicians are paid on a fee-for-service basis, according to fee schedules negotiated between the professional associations of health insurance fund physicians and the regional associations of health insurance funds.

Usually, West German physicians work entirely either in private practice or in a hospital. The dichotomy between ambulatory and in-patient practice is statutory and strictly enforced, and has a number of peculiar consequences. First, most hospitals are prohibited from operating out-patient departments, because the provision of ambulatory care is the preserve of physicians in private practice. Hospitals may intrude on this monopoly only if they are affiliated with a medical school and their out-patient clinic serves a teaching function. Second, a private physician sending a patient to a hospital loses both medical and economic control over the patient during the latter's hospital stay.

PRENATAL SCREENING

No prenatal screening programme in the FRG screens all pregnant women. However, women at known risk of producing a child with a severe genetic

[1] References p 66.

disease or congenital malformation because of advanced maternal age (≥35 years), a previous child with a severe genetic disease or congenital malformation, or family history of such disorder are offered prenatal genetic *diagnosis* services.

At present, mid-trimester prenatal genetic diagnosis is an established routine in antenatal care in the FRG and a recognised standard of care in obstetric practice. The costs of prenatal genetic diagnosis are covered by the West German health insurance ('sickness') funds. The following major techniques are in use.

Ultrasonography

Ultrasonography is used to examine the fetus to establish the gestational age, to locate the placenta and fetal structures, and to assess fetal viability. Ultrasound is used at two levels. First, it allows direct examination of the external and internal anatomy of the fetus and the detection of skeletal and other major organ system malformations. Second, it enhances the safety and effectiveness of invasive techniques such as chorionic villus biopsy, amniocentesis and fetal blood sampling.

The most widely used obstetric imaging is provided by real-time scanners. According to the Westphalian perinatal study 83.9 per cent of all pregnancies in 1984 were screened by ultrasound before the 21st week of gestation.

Mid-trimester transabdominal amniocentesis (amniocentesis)

Amniocentesis cannot be performed safely before 16 weeks of gestation. (Amniocentesis as early as the 10th week of gestation is still experimental.) During amniocentesis, cells shed by the developing fetus are extracted from a sample of amniocentesis fluid withdrawn from the expectant mother's uterus by means of a hypodermic needle. The cells are cultured and then tested for chromosomal defects and some biochemical defects. In addition the DNA of these cells can be analysed directly to identify specific genetic errors. Amniocentesis is the most commonly used invasive prenatal genetic screening technique: in 1986, 31,180 amniocenteses were performed in the FRG.

Chorionic villus sampling (CVS)

CVS is a relatively new and still experimental method of prenatal diagnosis which has been used since 1984/5 in the FRG. This technique provides results as early as the 9th week of pregnancy. Of the two (transcervical and transabdominal) methods of obtaining chorionic villus samples, the most commonly used method in the FRG is transcervical aspiration of chorionic tissue via a flexible catheter (Portex, Angiomed, Intracath, Down etc). Chorionic villus tissue has been shown to be suitable for cytogenetic, biochemical and DNA analyses. Preliminary results can be obtained within a day. More than 5000 CVSs have been performed in the FRG since 1984/5 (see *Table 3*, later). Late CVS for rapid karyotyping in the second and third trimester in high-risk pregnancies has been gaining impetus since 1987.

Table 1
Provision of prenatal genetic diagnosis in the FRG in 1986 in different types of laboratory

Provider	No.	Amnio %	CVS %
University-based institute	26	51.1	87.9
University-based hospital	7	6.5	1.4
Other hospitals	6	9.2	1.9
Public health facility	4	1.7	none
Private practitioners	16	31.5	8.8
Total	59	100	100

Source: Schroeder-Kurth T. Versorgung der Bevölkerung der Bundesrepublik mit humangenetischen Leistungen: Beratung und Diagnostik. *In* Schroeder-Kurth T (ed). Medizinische Genetik in der Bundesrepublik, Frankfurt/Main 1989.

Alpha-fetoprotein (AFP) measurements in amniotic fluid and maternal serum for neural tube defects (NTD) and Down's syndrome

NTD have an estimated incidence at birth in the FRG of 1.0 to 1.5 per thousand. When elevated AFP concentrations in amniotic fluid were found to be an indicator of the presence of open NTD, prenatal diagnosis became available. As AFP diffuses trans-amniotically into the maternal circulation, maternal serum AFP determination is a suitable means of screening for NTD during the mid-trimester. Maternal serum AFP screening and amniotic fluid AFP screening for NTD are offered in high-risk pregnancies. Analysis for low AFP serum levels, which may indicate a fetus with Down's syndrome, have been performed at some centres since 1986, in which year 282 cases were reported. Presumably the numbers are increasing rapidly.

Fetoscopy and fetal blood sampling

The main objects of fetoscopy are fetal blood sampling, tissue biopsy and fetal visualisation. The earliest possible gestational age for fetoscopy for fetal blood sampling is 17 weeks, while that for fetal visualisation is 15–17 weeks. The improved resolution of ultrasound has allowed development of a technique for fetal blood sampling under ultrasound guidance rather than under direct endoscopic visualisation.

Fetoscopy and fetal blood sampling are still associated with a relatively high pregnancy loss (5 per cent), maternal complications (4 per cent) and preterm labour (10 per cent). These methods are therefore restricted to a relatively small number of high-risk pregnancies.

HISTORICAL BACKGROUND TO THE IMPLEMENTATION OF PRENATAL GENETIC DIAGNOSIS IN THE HEALTH CARE SERVICE OF THE FRG

Legacy of the Nazi regime

In post-war Germany human genetics was totally discredited by its use in the service of the Nazi state. Prominent German human geneticists had actively participated in spreading Nazi race ideology, declaring Jews to be foreign genetic material that had to be removed from the German people. A eugenic sterilisation law had made sterilisation compulsory for a variety of illnesses thought to be genetic in origin. Thousands of children born with severe birth defects as well as mentally retarded adults were put to death in so-called mercy killings in the process of the 'euthanasia' programme. Thus after World War 2, human genetics as a scientific discipline not only had a very doubtful reputation but was also in a very fragmented state. It was scarcely represented in medical school curricula. Even as late as 1959 only four departments of human genetics existed in the FRG.[2]

One must bear in mind this dreadful heritage when one examines the public debate on controversial ethical and moral problems generated by the new prenatal genetic screening techniques. It is evident that the past still evokes special fears and mistrust.

THE LATE 1960s AND EARLY 1970s

The rapid developments in cytogenetics based on the research into the mutagenic effect of radiation and fallout, together with the steady improvement of ultrasonography in the late 1960s led to the belief that mid-trimester transabdominal amniocentesis was the most potent tool for the detection of chromosomal aberrations and inherited metabolic disorders.

The first amniocenteses in the FRG were performed in 1970, the initial impetus coming from the USA. At the 6th World Congress on gynaecology and obstetrics in New York (April 1970) Valenti, Kava, Jacobson et al. presented the techniques of genetic prenatal diagnosis for the first time to an international audience. Professor K Knörr (head of the Women's Clinic, University of Ulm) and his wife Professor H Knörr-Gärtner, a cytogeneticist, were conducting research in teratogenetics and mutagenicity and who were attending the congress decided to begin an amniocentesis service for prenatal genetic diagnosis at in Ulm. Because of their extensive cytogenetic research they had all the necessary laboratory equipment and manpower.

In 1970 they performed the first amniocenteses for obtaining fetal cells in Ulm on pregnancies that were scheduled for termination. The aim was to test the different available methods for the culture of fetal cells from amniotic fluid. As the methods applied could not be reproduced satisfactory, a modified technique developed by H. Knörr-Gärtner[3] was put into practice. Thus Ulm became the 'training centre' for most teams that wanted to introduce prenatal genetic diagnosis at other places in the FRG. Six amniocenteses were performed in 1970, 16 in 1971 and 49 in 1972.[4]

However, all the important elements for a successful installation of a prenatal genetic screening programme were missing. These include
a) reliable, safe and accurate standardised testing
b) laboratory quality assurance
c) adequate manpower/staff
d) provision of diagnostic services such as genetic counselling and abortion services
e) financing of the services/funding to establish and maintain a programme
f) a firm administrative base
g) professional and public education.

The then existing departments of human genetics at the medical schools were small and understaffed, and because human genetics was not represented at every medical school their location was erratic. A network of medical and non-medical scientists who were pioneering in prenatal genetic technology was organised by Prof Knörr in Ulm and Prof J Murken in Munich. The objective was to overcome the obvious obstacles which beset the further provision of amniocentesis within the then existing health care facilities:
a) Amniocentesis at that time was absolutely experimental. There existed no data about the risks of amniocentesis for the fetus and for the expectant mother.
b) Nothing was known about the reliability and accuracy of the cytogenetic findings, or the efficacy of the method as a whole.

To obtain these data a substantial amount of amniocentesis had to be carried out and laboratory performance had to be calibrated. But there were not enough laboratory facilities or trained manpower to expand the number of amniocentesis adequately. Until then, only a handful of experienced scientists and technicians could perform cytogenetic and biochemical analysis and very few obstetricians with the skill to perform mid-trimester amniocentesis. Additionally there existed the problem of how to incorporate amniocentesis in the existing health insurance fund schemes. As a preventive measure it was not considered a curative treatment and accordingly was not reimbursable.

Thus those medical geneticists/obstetricians who wanted to incorporate amniocentesis into prenatal care had to:
a) raise funds to develop amniocentesis into a standard procedure and to secure the necessary scientific and technical staff;
b) lobby outside their scientific community to gain support of decision makers in health care provision;
c) convince the public that amniocentesis was a useful and necessary technique within health care because individual patients as well as society at large would benefit from it.

But the effectiveness of prenatal genetic screening depended not only on its ability to detect affected fetuses but on the provision of follow-up services including genetic counselling, high risk prenatal management including parental choice. At that time only a few departments of human genetics offered genetic counselling, while genetic counselling centres did not exist. To make matters worse, it was illegal to terminate a pregnancy for genetic reasons or because of fetal abnormality.

These problems were tackled at the first scientific meeting on genetic diagnosis in pregnancy, organised in Munich in November 1970 by Knörr and Murken. The meeting was covered by the press (Süddeutsche Zeitung). This was one of the earliest media coverages in the FRG of the availability of amniocentesis, including an account of how the regulations on termination could be legally circumvented by means of a psychiatric report stating that the mother would suffer from irreversible mental trauma if she had to carry the pregnancy to term. The article in the Süddeutsche Zeitung ended with Murken's belief that prospective parents had the right to be informed to the full extent of current knowledge in prenatal care.[5] The proceedings of the conference, including a paper on the medicolegal aspects of the termination after amniocentesis, were published.[6]

Discussions on liberalising the abortion law, including the option of terminating a pregnancy with a severely handicapped fetus

The late 1960s and early 1970s in the FRG were characterised by active social movements to change a society regarded as too conservative, unable to cope with structural and socio-political changes regarded as necessary. For the first time after the second world war a coalition of the social democratic party and the liberal party came into power. As far as the development of prenatal genetic screening was concerned this political change meant that the restrictive abortion law (218, Civil Penal Code) would be reformed and liberalised.

As the new government went to work on that reform there were efforts by progressive political groups to include in the re-wording of Code 218 the legalisation of the abortion of a severely affected fetus. Thus the 'Humanistische Union', a political organisation, claimed that the freedom to choose abortion in cases of fetal malformation was a fundamental woman's right.[7] For other groups, especially the legal profession and theologians, the discussion about this special abortion topic seemed to be an uneasy one marred by the experience with the Nazi eugenic laws.

This may be illustrated by a statement[8] made in 1972 by Krauss, who held a chair on philosophy of the law: 'The reasons for caution in re-wording Penal Code 218 for preventing the birth of severely handicapped children include: the bitter legacy of the law on hereditary health passed during the Nazi period; the antipathy towards "positive eugenics" aiming at a general improvement of hereditary factors; the uncertain and contradictory statements of psychiatry as to the hereditary properties of mental diseases; the fact that contraception and sterilisation are methods both effective and humanitarian for prevention of hereditary defects; and the general doubt whether the destruction of incipient human life can be sufficiently justified at all.'

Both Catholic and Protestant churches were opposed to the legalisation of abortion of a fetus with a severe genetic disease or malformation, as were a substantial number of obstetricians – although apparently not the majority of them, as a vote by their professional board at that time demonstrated.[9]

Early public support of prenatal genetic screening technologies

In the early 1970s the new genetic screening technologies were hardly known to the public. Occasionally daily newspapers, directly informed by those working in the field, provided coverage in which prenatal diagnosis was considered to be a promising new technology and to be beneficial.[10]

Promoters of the new techniques considered education of the public to be very important. They lectured for lay audiences, made radio and television broadcasts,[11] and collaborated in the production of new textbooks for German secondary schools. When the German Genetics Society held its 4th annual meeting in 1972 in Freiburg/Breisgau it held a public round table discussion on genetic, medical, legal and ethical aspects of the early diagnosis of human genetic anomalies. Some of the most prominent scientific journalists in the FRG (Deich of 'Die Welt', Flöhl of 'Frankfurter Allgemeine Zeitung' and von Randow of 'Die Zeit') were invited to participate in the discussion. Among the other participants were an expert in judicial problems from the Federal Ministry of Justice, which was then working on reform of the abortion law, and a professor of ethics and sociology, who was also a member of the Dominicans (a Catholic order).

At that time prenatal genetic screening was supported both by leading representatives of the main organisation of the mentally handicapped 'Lebenshilfe'. In June 1973 a wealthy member of the governing board of this organisation made a 350,000 DM donation in support of research on 'the clinical application of prenatal genetic diagnosis techniques'. The donation was allocated to the head of the genetics laboratory at the University of Munich (Murken), and a genetic counselling centre which offered prenatal genetic screening services – the first one in Bavaria – was installed with it. The ceremony of the handing over of deed of gift was attended by prominent scientists (eg Nobel prize winner W. Heisenberg), members of the Bavarian Parliament and the founding fathers of the 'Lebenshilfe'.[12]

When the proceeds of this donation were about to run out, members of the Bavarian parliament and senate, as well as the president of the Federal chamber of the medical doctors appealed to the Bavarian government to continue the funding via the state budget. These interventions were successful and in 1975 Bavaria became the first state in the FRG to provide public funding of prenatal genetic screening services.[14]

The multi-centre collaborative study on diagnosis of genetic defects, 1973–9

The most important step in the introduction, implementation and diffusion of prenatal genetic screening in the FRG was taken in 1972, when the Deutsche Forschungsgemeinschaft (German Research Society) decided to make a multi-million DM grant for a 7–year multi-centre collaborative study on diagnosis of genetic defects as a priority programme.

The DFG, founded after World War 1, is the most important research foundation in the FRG; it not only makes grants but advises parliaments and public authorities on scientific matters.[14] In 1988 the DFG had an annual

budget of 1,122 million DM at its disposal; of this sum, the Federal Government provided 680.2 million and the Länder (States) 435.3 million, 4.7 million were received from foundations and 2.8 million came from the society's own resources.

The application for the priority programme grant was prepared by a group of scientists actively involved in research on prenatal genetic diagnosis, including especially Professor H. Knörr-Gärtner, now head of a committee on mutagenicity, and Prof Bresch, who held a chair in genetics and molecular biology at the University of Freiburg. The DFG invited some 30 scientists from all over the FRG holding chairs in molecular genetics, human genetics and obstetrics and who were known to be ready to work in the field to a working party in March 1972. Before the meeting a detailed questionnaire was sent to the participants requesting views on: international scientific standards and knowledge in prenatal diagnosis of genetic defects; priorities in the development of diagnostic methods; existing capacity, know-how and manpower in prenatal diagnosis in the FRG and predicted need to meet demand until 1980; how many diagnostic procedures had already been carried out; what the ideal centre for prenatal diagnosis should contain and where it should be located; what genetic counselling and abortion services were needed; costs; how many centres would be needed in the FRG; time required to recruit and train the necessary manpower, with costs; whether private practitioners should be included in the programme; and which laws needed to be revised. The working meeting gathered the information, produced an overview together with a commentary and recommendations, and two months later (at the above-mentioned 4th annual meeting in Freiburg) produced a consensus final research proposal.

Prominent foreign scientists were invited to attend this annual meeting, with two objectives in mind, partly because prenatal genetic diagnosis in the FRG was always conceived of as part of an international cooperation which would benefit from international experience, and partly because a subcommittee of the DFG planned to hold an international scientific hearing on the organisation of a prenatal genetic diagnosis programme in the FRG immediately after the meeting.

Prior to the hearing a questionnaire was sent to the invited foreign scientists, as follows:

1 Estimates of demand for prenatal diagnosis. On what data would you base a prognosis for the next ten years?

2 What steps have been taken, and by whom, to familiarise the general public of your country with the problems involved? What response is to be expected from publicity campaigns?

3 What is the best way of organising facilities for performing prenatal diagnosis, regarding

a) size of units for routine work – personnel and equipment necessary;
b) desirability of concomitant research work – personnel and equipment necessary;
c) correlation between clinical and diagnostic work; sponsoring body (government, private initiative, university-associated)?

4 Is there any effort to co-ordinate – nationwide or within a given

period – the distribution of specialised facilities, as a convenience for the public? (Is there any experience in air transport of cells in amniotic fluid?)

Is it meaningful to attempt such co-ordination on an international scale?

5 Are there efforts to co-ordinate data collecting (ie standard forms, standard follow-up procedures, etc)?

6 What are the most important aspects of the future research regarding

a) improvement of existing surgical procedures
b) improvement of existing diagnostic techniques
c) development of diagnostic assays for hereditary defects not as yet diagnosable prenatally
d) development of totally different techniques for prenatal diagnosis (for instance 'uteroscope' for detecting anatomical malformations, etc)?

The participants invited to the hearing were: D Bergsma, USA; K Boczkowski, Poland; J H Edwards, UK; C B Jacobson, USA; V A McKusick, USA; M Mikkelsen, Denmark; J E Seegmiller, USA.

The priority programme was approved by the DFG senate in November 1972. Since it required a substantial amount of money immediately which outstripped the available funds, a one-off 500,000 DM donation was obtained from the West German concrete industry via the 'Stifterverband für die deutsche Wissenschaft' (West German industry's association for the financial support of science). An additional indicator of the importance the DFG senate attached to the promotion of prenatal diagnosis is the fact that it agreed to finance the specific costs stemming from the provision of prenatal genetic diagnosis services which were not reimbursable by the health insurance funds.

The aims of the programme were twofold:

1 *To evaluate the safety, accuracy and reliability of prenatal genetic screening via amniocentesis.* This entailed collecting data on:

a) Diagnostic measurements, such as fetal karyotype analysis, fetal sex determination, AFP measurement in amniotic fluid, diagnosis of fetal metabolism.
b) Preparation and performance of amniocentesis, including: outpatient/hospital procedure, blood grouping, assessment of gestational age, placental localisation, visualisation of the fetus, amniocentesis in twin pregnancies, site of the tap, size of the needles used, utilisation of ultrasound, examination of quality of amniotic fluid samples, feasibility and effect of repeated amniocentesis, examinations immediately after amniocentesis.
c) Follow-up of pregnancies after amniocentesis, such as:
complications after amniocentesis, spontaneous abortions after amniocentesis with embryopathological investigation, stillbirths after amniocentesis, pregnancy termination due to prenatal diagnosis and investigation whether prenatal diagnosis was confirmed, live births after amniocentesis, congenital malformations prevalent at birth, skin scars, neonatal death.

2 *To introduce prenatal genetic diagnosis services at special centres.* This was done by establishing cytogenetics laboratories, mainly at university departments and university hospitals, staffing and equipping them appropriately, and offering prenatal genetic diagnosis to all at-risk pregnant women who

had access to or were referred to these centres and gave informed consent. Thus, the study was not confined to a defined sample size, and no control groups were included in the study design.

Over 90 departments of obstetrics, paediatrics and human genetics in 34 towns including West Berlin joined the programme. When the programme ended, more than 100 scientists and medical doctors had been trained with study funds and were familiar with the technology. More than 13,000 pregnancies had been screened. Thus when the programme ended it had completely fulfilled its goals: amniocentesis had become a reliable and safe procedure, and prenatal genetic diagnostic services and follow-up services (eg genetic counselling) had been established in at least 41 prenatal centres all over the FRG and West Berlin. Thus the structure to provide prenatal genetic diagnostic services in specialised university-based centres had been shaped.

Table 2 shows the dramatic increase of number of amniocenteses performed in the FRG during the study.

Table 2
Number of prenatal diagnostic cases 1970–7

1970	6
1971	16
1972	49
1973	112
1974	308
1975	893
1976	1798
1977	2648

Source: 15; Informationsblatt über der Dokumentation des Schwerpunkt-programms 'Pränatale Diagnostik genetisch bedingter Defekte' der Deutschen Forschungsgemeinschaft, Munich 1981.

During the study the proportions of the different indications for amnio-centesis changed markedly. When the study started in 1973, the indication 'advanced maternal age' represented 43.6 per cent of the total, 'previous child with chromosomal aberration' 28.4 per cent and 'parental carrier of a balanced chromosomal aberration', 5.5 per cent. The proportion of those obtaining amniocentesis on the indication 'advanced maternal age' steadily increased, up to about 80 per cent of all amniocenteses performed in the FRG in 1979, so that the percentage obtained on other indications decreased to 2.6 per cent and 0.3 per cent respectively. These proportions have remained constant up to the present. (*Source: op cit.*)

THE MID-1970s AND EARLY 1980s

The steady increase in utilisation of prenatal genetic diagnosis was also due to the following structural changes which facilitated the accessibility and availability of prenatal genetic diagnoses services in the FRG:

a) Since 1975 the costs of prenatal genetic screening and genetic counselling have been covered by the FRG health insurance funds.
b) Since 1976 the 218 Civil Penal Code legalises the interruption of pregnancies up to the 22nd week of gestation if the fetus is found to be 'defective' and the pregnant woman wishes to terminate the pregnancy.
c) Direct state government financial support (mainly of the state universities) has allowed expansion of prenatal genetic screening and genetic counselling services. Cytogenetic laboratories and genetic centres were installed, predominantly at medical schools, on the following dates: Bavaria 1975; North-Rhine-Westphalia 1976; Schleswig-Holstein 1977; Baden-Württemberg 1978; West Berlin, Lower Saxony 1979; Bremen 1979.

A tide of medical and legal opinion in the FRG steadily forced the recognition that prenatal genetic screening was a standard part of quality care. The first successful legal action for malpractice was brought[15] by a couple not offered this service to whom a child with Down's syndrome was born. More physicians and obstetricians became aware that they were vulnerable to such actions if they failed to take into account, or act upon the knowledge of, an increased risk of the birth of an infant with physical or mental abnormalities.

Primary health care providers continued to be ignorant about genetics and the new techniques, so that one of the priorities of the genetics community was to lobby for adequate education in genetics for private practitioners.

In 1976 the federal association of health insurance funds, whose function is to uphold the standard of medical care provided by private practitioners for contributors to the health insurance funds, published detailed information about prenatal genetic diagnosis in its bulletins.[16] This publication notified every practising health insurance fund physician about the availability of this procedure, target groups, and the legal background to abortions.

As more pregnant women became aware of the existing prenatal genetic diagnosis services and more obstetricians referred patients to them, the demand for prenatal diagnoses outstripped the laboratory facilities of almost all centres. Waiting lists grew, and latecomers ran into difficulty in obtaining amniocentesis. The consequent consumer pressures improved access and availability by forcing the 'Land' of North Rhine-Westphalia, for example, to increase manpower at the cytogenetics laboratory at the Medical School of Münster.

With the increasing numbers receiving amniocentesis and prenatal genetic counselling, the professionalisation of the service also increased. In 1978, medical genetics was acknowledged as a medical specialty by the certification board.

Health policy decisions regarding the prenatal genetic screening services

In 1977 the conference of the State secretaries of health of the FRG recommended[17] that the prenatal genetic diagnoses services installed and funded by the DFG should be maintained financially after that funding ceased (in 1979); that the capacity of the prenatal genetic screening services in the FRG should

be enlarged to ensure that all pregnant women at increased risk could obtain amniocentesis; and that departments of human genetics should be set up in each medical school in the FRG.

In 1978, one year before the DFG funding ended, the 81st annual meeting of German physicians put prenatal genetic screening on its agenda, covering the following issues:[17]

a) what prenatal genetic screening can achieve and what are the indications for it
b) future facilities needed to meet expected demand
c) the recommendations of the conference of State secretaries of health and their implementation by the State governments; a recent survey had shown[18] that all states had agreed to continue to fund services once the research money was exhausted
d) cost-benefit analyses of prenatal genetic screening
e) ethical problems related to prenatal genetic diagnosis.

Very probably, these issues were put on the agenda in order to ensure that prenatal genetic diagnosis and the centres providing the services secured professional and public attention at a time when continued funding hung in the balance, and was dependent on state health policy decisions. To ask the states to step in and fund an outpatient medical service at its medical schools is unusual in the FRG health care system, in which most outpatient services are typically delivered by private practitioners. But because of the scarcity of the special skills required and the fact that there was likely to be little profit to the practitioners, there was no alternative, and prenatal genetic diagnosis has remained a special service at university level to the present day ([19]; see also *Table 1*).

The collaborative study of maternal serum AFP screening for neural tube defects (NTD)

In 1979–82 a collaborative study of maternal serum AFP screening for NTD screened more than 50,000 pregnancies. This study was stimulated by the results of the corresponding UK collaborative study. The aim was to provide reliable screening parameters for the FRG. In contrast to the British study, an unselected sample of pregnancies in a low prevalence (1.0–1.5 births per thousand) population was screened.

The conclusion was reached that general screening for NTD in the FRG was feasible, it could be effectively implemented and could be cost-beneficial. But, as its authors recommended:[19] 'As long-term screening of the whole (pregnant) population cannot be established, maternal serum AFP measurement in the second trimester is recommended for pregnant women who are at increased risk for fetal NTD but refuse amniocentesis, or for those whose risk is not high enough to justify amniocentesis as a primary method.'

Utilisation of prenatal diagnosis in the early 1980s

Utilisation of amniocentesis rapidly increased in the early 1980s; CVS figures began to be collected in 1985 (*Table 3*).

Table 3
Prenatal diagnoses performed in the FRG, 1970–87

Year (documented years only)	Amnio No.	CVS No.
1970–73	193	–
1974	308	–
1975	893	–
1976	1 798	–
1977	2 648	–
1978	3 925	–
1982	15 838	–
1984	22 506	[No data]
1985	26 130	926
1986	31 180	2092
1987*	33 535	3100

* Estimated Schroeder-Kurth, see *Table 1* reference.

Most amniocenteses and CVSs (approximately 80 per cent) were performed on the indication of advanced maternal age. Although there were differences of opinion on what maternal age should be the cut-off point, it was arbitrarily agreed that a mother below 35 years of age should not obtain amniocentesis on this indication.

This cut-off point led and still leads to strong consumer pressure by pregnant women younger than 35, who are afraid of bearing a child affected with a chromosomal aberration. Especially feared is Down's syndrome.[20] Today 'maternal anxiety' (regarded by most genetic counsellors as a so-called placebo indication or a so-called non-medical indication,[21]) accounts for 10–15 per cent of all prenatal diagnoses performed in the FRG. The health insurance funds do not object as long as their practitioners certify that prenatal diagnosis is necessary.

Although it is estimated currently that about 50 per cent of all women eligible for prenatal genetic diagnosis on the indication of maternal age obtain it, Table 4 shows that, taking the FRG as a whole, 60 per cent of women eligible for prenatal diagnosis were not obtaining it in 1985.

In 1983–85 a socio-epidemiological utilisation study conducted by the department of human genetics, Münster medical school, revealed[22] that women obtaining amniocentesis on the indication of advanced maternal age came predominantly (76.6 per cent) from the middle and upper middle classes. These women tended to be a highly educated group (university degree or extensive vocational training 58.8 per cent) and were living in urban or suburban areas (69.5 per cent). These women seemed not to be merely better informed about the availability of prenatal genetic diagnostic services but it also seemed highly probable that they decided on their own initiative that prenatal diagnosis might be relevant for their family planning situation. For the less educated women coming from the lower social strata,

Table 4
Utilisation rates of prenatal diagnosis on the indication of advanced maternal age (› 35 yrs) in the different States of the FRG in the early 1980s

State	Year 1982 %	Year 1984 %	Year 1985 %
Schleswig-Holstein	36	36	40
Hamburg	96	89	99
Niedersachsen	10	11	14
Bremen	100	100	87
Nordrhein-Westfalen	24	28	30
Hessen	24	35	47
Rheinland-Pfalz	22	37	51
Baden-Württemberg	36	56	66
Bayern	17	25	30
Saarland	19	23	28
Berlin	53	63	73
FRG	29	35	40

Source: Schroeder-Kurth, *see* Table 1.

the obstetrician played an important role in initiating prenatal diagnosis. But as this study showed, more than half (52.8 per cent) of the private practising insurance obstetricians within the study area were not referring a patient for amniocentesis, in contrast to only 17.8 per cent of the insurance obstetricians working at a hospital. Thus, obstetricians' referring behaviour heavily influenced amniocentesis utilisation, to the disadvantage of the women coming from the lower social strata.[22]

THE MID-1980s TO THE PRESENT

Despite some disagreements (ie whether maternal anxiety should be regarded as an indication for prenatal diagnosis), a consensus professional philosophy held by medical geneticists/obstetricians providing prenatal genetic screening services clearly emerged in the mid-1980s and became instrumental in setting up guidelines as to how quality prenatal genetic screening should be performed and provided in the FRG. These guidelines were laid down in 1987 as recommendations of the scientific advisory board of the chambers of physicians at federal level.[23] The quintessence of these guidelines is to restrict quality provision of prenatal genetic screening techniques and methods to special obstetrical centres collaborating with medical genetics, paediatricians, paediatric surgeons etc. Genetic counselling prior to as well as after the screening if findings are positive is regarded as indispensable. The guidelines also emphasise the autonomy of the individual decision of the patient and state that the freedom of reproductive choices includes the freedom to carry a

fetus with a serious genetic defect to term.

As prenatal genetic technologies and services became more complex and more widely used in the 1980s, more difficult moral and ethical dilemmas became apparent to a wider public. A vast amount of literature about ethical, medicolegal and social problems inherent in the new technologies and their scope of application steadily accumulated, indicating how important these issues are to the public.

The public discussion on ethical problems in prenatal genetic in the FRG covers a wide spectrum of controversial issues, such as:

a) abortion choices over a wide range of severity in some diagnosable genetic disorders, some of which are treatable[24]
b) claims that mid-trimester abortion creates precedents for paediatric euthanasia
c) controversial indications for prenatal diagnosis such as sex choice unrelated to sex-linked disorders, and other potential misuse ('slippery slope' argument[25])
d) fear of the revival of eugenic policies and coercive public health programmes[26]
e) reduced social acceptance of disabilities.[27]

Disability organisations and churches especially express these fears and are asking for a critical evaluation of the social impact of prenatal genetic diagnosis. Even the representatives of the 'Lebenshilfe' (the organisation that helped to establish the first prenatal genetic diagnosis and genetic counselling centre in Bavaria in the early 1970s) voice their reservations concerning prenatal genetic diagnosis today.[28]

As CVS, which makes fetal sexing possible in the first trimester of pregnancy, became available in 1984/5 in the FRG the professional organisation of medical geneticists, fearing potential misuse of prenatal diagnosis for sex selection unrelated to sex-linked disorders tried to exert moral guidance by founding an ethics board which recommended with-holding information about sex of the fetus until the 14th week of gestation.[29]

Radical feminist groups demanded (and still demand) the closing of all prenatal genetic diagnosis and counselling centres and the cessation of all prenatal genetic diagnosis.[30] Although these groups do not oppose abortion in general, they are against abortion of affected fetuses. This somewhat contradictory standpoint is arousing controversial discussion within feminists groups, especially within the so-called Greens. Militant underground groups like the terrorist 'Rote Zora' threaten genetic counselling and research centres as well as obstetricians providing prenatal genetic diagnosis. In 1985 the genetic counselling centre at Münster medical school was completely destroyed by a time-bomb planted by the 'Rote Zora'.

Prenatal genetic screening and public health policies in the middle and late 1980s

Health policy in the FRG clearly supports prenatal genetic screening:

a) by governmental funds: more than 15 million DM were granted by the federal minister for a collaborative study on the development and evaluation

of CVS, to run from 1985 to 1990. More than 27 university centres are participating. The organisational aim of the study is the same one as in the amniocentesis DFG study: to assess the risks of CVS, to calibrate the procedure, to train manpower and to implement CVS as a routine within the provision of prenatal obstetric care. Mostly the same centres and the same scientists that promoted amniocentesis have planned and set up the multi-centre study. They were explicitly opposed to a randomised clinical trial study design to evaluate CVS.[31]

b) by supporting and explicitly favouring the existing structure of prenatal genetic diagnosis services at a limited number of highly specialised centres, that provide follow-up services such as genetic counselling (eg [32]).

To assess the new genetic screening technologies the Bundestag (federal parliament of the FRG) set up in 1985 a commission on chances and risks of genetic technologies. The report of the commission[33] called on the federal parliament, the federal and state governments and the medical professional organisation to ensure that:

a) genetic counselling and prenatal genetic screening remains non-mandatory for prospective parents
b) prenatal genetic screening does not generate social pressure to abort affected fetuses
c) genetic counselling is provided as an indispensable prerequisite to prenatal genetic diagnosis
d) genetic counselling is done exclusively by genetic counselling centres (quality assurance)
e) psycho-social follow-up services are provided
f) the manpower and technical capacities of present services are expanded.

Opposition votes were recorded by two committee members, one belonging to the Green Party the other one belonging to the Lutheran Church.

The provision of prenatal genetic diagnosis today

The process of implementation of prenatal genetic screening into the mainstream of prenatal primary care in the FRG is not yet complete. Approximately half of all pregnant women eligible for prenatal diagnosis on the indication of advanced maternal age do obtain it today; some urban areas have higher utilisation rates but some rural areas have very much lower ones.

Whether the existing utilisation of prenatal diagnosis has any impact on the prevalence of genetic diseases/congenital malformations can only be estimated. Probably it has not much yet. For instance: 8 per cent of all children born in the FRG, and about 40 per cent of all children born with Down's syndrome, are born to mothers who are 35 years of age or older. If 50 per cent of these at-risk women receive prenatal diagnosis and all those in whom an affected fetus is found choose to terminate the pregnancy, the incidence of Down's syndrome will be reduced by only 20 per cent.

It is estimated that there are still social inequalities in utilisation despite there being no economic hindrances to access to prenatal diagnosis services.

Today the provision of CVS is rapidly increasing. Two centres were active in introducing CVS in the FRG: Ulm (provided in 1983 the first training

session for CVS in West Germany) and Münster (technique brought back from the USA in 1982/83). A collaborative multi-centre randomised study of CVS is financed by the prenatal care and obstetrics programme of the ministry of research and technology.

The great advantage[18] of CVS over amniocentesis is that it can be done much earlier in pregnancy, at about 8–10 weeks, with results available within 24–28 hours, whereas amniocentesis results take about 3–4 weeks. If the fetus is found to be affected, women choosing to abort the pregnancy can undergo a first-trimester abortion, with lower risks of maternal morbidity and mortality. These obvious advantages are still flawed by the absence of precise data on the risks of the procedure and the background risk of spontaneous abortions in pregnancies at the gestational age at which CVS is performed. Data from the multi-centre CVS study in the FRG clearly indicate that with increasing experience and numbers of CVS performed, the number of spontaneous abortions after CVS decline dramatically. Centres with more than 2000 CVS performed report that their risk figures do not differ significantly from the risk rates reported in the Canadian randomised study and the NIH study (additional risk estimated at 0.5–1.0 per cent).[34]

The major concerns about the future of prenatal genetic diagnosis stated by medical geneticists [35, 36] are that allowing free market principles to operate in genetic services (eg providing genetic test kits) would substantially affect the quality of counselling services. However, the main limitation on incorporation of prenatal DNA testing into primary health care is still expected to be the lack of knowledge which primary care providers have in this area.

CONCLUSIONS

When, approximately two decades ago, prenatal genetic diagnosis started in the FRG all the important elements for a successful screening programme (reliable, safe, standardised testing, laboratory quality assurance, adequate manpower and laboratory facilities, financing of the services, provision of additional diagnostic services such as genetic counselling, professional and public education) were missing and had to be developed. The future providers of the prenatal diagnostic services – medical geneticists, cytogeneticists, paediatricians, specially trained clinical geneticists and some obstetricians – clearly dominated the implementation process.

They successfully allocated research grants to implement amniocentesis, they successfully lobbied health care decision-makers on state and federal government level. They developed a special philosophy on how prenatal genetic diagnosis and counselling should be provided in the FRG which gained the support of health care policy makers. Today the favoured scheme is to restrict prenatal genetic screening services to highly specialised centres which maintain high standards in the provision of collaborative services and follow-up care. These centres are expected to set the standards in regard to quality and ethical aspects in care and research. The commercial development of prenatal screening services is regarded with concern by medical geneticists. Only a handful of unattached practising physicians provide laboratory services in prenatal genetic diagnosis.

The need and demand for prenatal genetic diagnosis services (including clinical evaluation, counselling, specialised laboratory testing, treatment and referral) will continue to grow in the FRG. With the rapidly expanding diagnostic possibilities due to molecular genetics, prenatal genetic screening services will continue to raise important public health issues such as voluntary, not mandatory approach to genetic screening, accessibility of the services especially for minorities, and prenatal diagnosis for non–medical reasons.

A special feature of the FRG is that many medical geneticists consciously avoid any suspicion of eugenic considerations and display a general confidence about resolving ethical problems at the individual–family level.[21] To shy away from societal and political issues when increasingly powerful diagnostic genetic technologies emerge and to locate the problem on individual decision–making may well prove problematic as well.

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DIFFUSION OF PRENATAL SCREENING IN SWEDEN, WITH EMPHASIS ON DOWN'S SYNDROME AND NTD DEFECTS

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ORGANISATION AND FUNDING OF HEALTH SERVICES IN SWEDEN

Local organisation and administration of health care is mainly the responsibility of the County Councils, which also have the right to levy a special tax mainly used to fund health care. At present 9 per cent of the Swedish GNP is spent within the health care sector. The County Councils together form a national central organisation with considerable power to direct how specialist resources should be used uniformly over the country.

The country is divided into six regions, each with a regional hospital where every kind of subspecialty should be available. These regional hospitals are all university hospitals with teaching and research activities.

Antenatal care is in general part of primary health care, but each county hospital has a referral out-patient clinic for pregnancies with complications where all kinds of prenatal diagnosis are also offered. The rarer complications are referred to the regional hospital, where special expertise in genetics and ultrasound diagnosis is available.

Antenatal care is 100 per cent accepted and expected by pregnant women of all ages and social classes. A very small part is outside the public sector. There is a high degree of uniformity in the general antenatal care programme.

The government takes part in the development of health care mainly through legislation within the social security system. The National Board of Health and Welfare (NBHW) has played a leading role as the highest authority on medical practice and as a control organ for all health personnel, but its influence in recent years has decreased.

Swedish health care is funded almost totally from taxation as part of the social security system. The patient's contribution is very small, with an upper limit of expense for medicines and health care for any given year for each person. All health care in pregnancy and at delivery is free. The private sector is small and again not expensive for the patient. Prenatal diagnosis is performed only in the public health sector except for ultrasound examinations in normal pregnancies.

HISTORY OF EVENTS

Down's syndrome and other chromosomal defects

The technique of cultivating fetal cells obtained by amniocentesis in the second trimester was first used in Sweden in 1970–1 in a limited number of cases, mostly with some known genetic risk of chromosome abnormality.

The first available national figure for prenatal chromosome diagnosis is for 1972 (90 cases).

In 1970 the first laboratory for clinical genetics opened at the Karolinska Hospital in Stockholm. In 1975 a second laboratory was opened in Lund. At that time a limited clinical genetic service, including chromosome analysis, was provided in three other university hospitals by laboratories which were started as research institutions and staffed mainly by means of research grants. In 1976, as part of an investigation of the need for health care in the 1980s by the NBHW, an expert group including leading clinical geneticists, stated[1] that the expected development of prenatal diagnosis was an important reason to devote more resources to clinical genetics. A number of indications for prenatal diagnosis were listed. No attempt was made, however, to estimate the number of tests necessary to meet these indications, and new indications were also anticipated because of the development of new methods. The organisational plan for a genetics service called for one department of clinical genetics in each of the six regions (1–1.5 million inhabitants). Each department would need a staff of at least 9–10 persons for the cytogenetics laboratory alone.

This plan was adopted and by 1981 all six regions had their genetic service organised, with five departments and two additional small laboratories. In 1985 their budget amounted to 14 million Skr, and they were staffed with ten specialists (two professors), four non-specialists, three and a half university staff and 60 technical/administrative staff.

Table 1
Utilisation of prenatal chromosome diagnosis since 1972

	Amnio-centesis	Chorionic villus sampling	Deliveries (1000s)	% >35yr
1972	90		112	6.9
1975	627		104	6.9
1979	2810		96	7.1
1980	3499		97	8.5
1985	4161	181	98	11.7
1987	4854	258	105	11.4
1988	5245	434	112	11.8

Clearly, the most pronounced increase in the number of fetal chromosome diagnoses occurred during the period 1975–80, coinciding with the increased capacity of the laboratory service. In the last 5-year period the rise in the number of examinations is more modest and some counties even report a slight decrease. The increase since 1980 may to some extent be related to a larger number of pregnancies in women over 35 years during this period.

There are no exact statistics concerning which indications led to these fetal chromosome diagnoses, but the genetics laboratories estimate that at present the maternal age is 35 years or above in about 75 per cent of cases, so that on

[1] References p 84.

average 40 per cent of pregnant women in that age group ask for the test when it is offered.

Chorionic villus sampling (CVS) in the first trimester was first used in clinical practice by Gustavii in Lund in 1984 using a transcervical technique. This technique was also introduced in Stockholm at the Karolinska hospital in 1985. Abdominal CVS was begun in 1985 in Lund and in 1986 in Uppsala. The number of examinations has steadily increased, so that 613 transcervical and 827 abdominal samplings were reported up to May 1989 from seven centres. The method was initially used mostly in cases where there was increased risk of a fetal genetic defect that might justify a late abortion. One limiting factor has been the high spontaneous abortion rate reported for the transcervical method. In a recent report by Gustavii *et al.*[2] a short-term miscarriage rate of 11.9 per 100 was found for the pooled data for transcervical CVSs in Sweden, as compared to 1.7 for the transabdominal. This experience will certainly limit further use of the transcervical technique in Sweden to a minimum.

Given the early booking into antenatal care in Sweden, CVS could become the dominant method for prenatal cytogenetic diagnosis, because of the well-recognised advantages of an earlier diagnosis.[2]

It is also important that a number of diagnoses of (mostly rare) genetic conditions can now be made on CVS samples using DNA probes. A total of 16 such examinations were performed in Sweden in 1987.

Indications for prenatal diagnosis

The first attempt to define a list of indications for prenatal diagnosis was made by the expert group working on the organisation of clinical genetics services[1]. The indications for prenatal diagnosis were listed by the expert group as:

a) elderly mothers (not defined)
b) chromosome anomaly in parents
c) X-linked recessive disease
d) increased risk of NTD defects, metabolic hereditary disease or muscular dystrophy
e) maternal anxiety for fetal defects.

In 1980–3 another expert group (including experts not only in genetics but also in embryology, obstetrics, paediatrics, medical psychology and medical ethics) was formed by the National Board of Health and Welfare and given the task of preparing a comprehensive report of current knowledge and use of prenatal diagnosis. Their report[3] included not only medical and technical aspects but also some economic estimates as well as psychological, ethical and law aspects of the problem.

This expert group proposed that enough resources should be made available to make possible voluntary prenatal diagnosis in cases with any of the following indications:

a) maternal age >37 years
b) selectively, 35–37 years

c) previous child with chromosome defect
d) other increased risk for chromosome defect
e) family history of detectable metabolic disease
f) family history of NTD.
g) but not sex determination, except on medical grounds.

This list was generally accepted by the various organisations and parties to whom the report was referred, and although the list has never been officially declared accepted policy by the government it has been widely adopted all over the country.

In the NBHW report the main indications used in clinical practice in 1981 were also described, and it was found that maternal age over 35 was the reason for about 80 per cent of the cytogenetic examinations. The indication that varied most over the country was maternal anxiety, being the main reason for the procedure in 30 per cent in some counties and hardly accepted at all in others. In 1985 only about 10 per cent of cases were stated as indicated by maternal anxiety. This may be a consequence of doctors keeping more strictly to medical reasons for diagnosis, but could also be due to swamping by an increased demand from elderly mothers with more awareness of this possibility. Another finding in the report was a close association between the number of examinations for prenatal diagnosis performed and the geographic distance from the hospital to the genetic laboratory. In the same region, the number of examinations performed relative to the number of pregnancies in women above 35 years could vary from a ratio of 0.87 for the area closest to the laboratory to 0.29 for a more distant one. This was ascribed mainly to lower awareness of both patients and doctors of the possibility of fetal diagnosis, but also to practical difficulties in sending either the patient or the sample a long distance. Since figures from different hospitals in the Stockholm area also show large differences in the use of fetal chromosome analysis, it seems more probable that doctors working in closer collaboration with the genetic laboratory tend to use the service more. The NBHWreport also confirmed differences in the attitudes of doctors towards advising the women to have an amniocentesis, see later.

NTD defects

The incidence of neural tube defects in Sweden is generally low: 0.4/1000 births for spina bifida and about 1/1000 births for all neural tube defects registered in 1970–80. The incidence was already decreasing in the period before prenatal diagnosis and consequent termination.

Soon after the possibility of using *AFP-values in maternal blood* as an indicator for fetal defects, especially NTD, was reported from the UK in 1972, the method was introduced by Professor B Kjessler. A research project was started using a simple paper disc radioimmununoassay (developed in Sweden) for AFP measurement. Between 1974 and 1976 this project offered maternal serum AFP determination between the 14th and 20th week of pregnancy in a number of antenatal clinics and in 1977 reported the results of 7158 cases studied.[4] Five out of seven cases with a NTD defect had an

elevated AFP value in maternal serum, but for various practical and organisational reasons a definitive diagnosis resulting in termination was arrived at in only one case. Incorrect gestational age was found to present the greatest problem for the correct interpretation of the result, and only 1.7 per cent of cases with an elevated AFP screening value eventually had a NTD defect diagnosed. The researchers, however, were enthusiastic about the association found between abnormal AFP values and some other malformations eg omphalocele, and also some other conditions carrying increased risk, eg multiple pregnancy, oligohydramnios and intra-uterine growth retardation.

A new project[5] was therefore launched (1978–80) in seven counties comprising a total population of almost 23,000 pregnant women, 80 per cent of whom agreed to participate. In 10 per cent of the cases the AFP test had to be repeated at least once, and in 0.9 per cent (range 0.19–1.90) amniocentesis was performed. The detection rate of open NTDs was better in this study, and 16 out of 21 possible cases were diagnosed during the second trimester, 14 of which were terminated by legal abortion. It was confirmed that organisational inadequacies always exist that will result in cases not being followed up as intended in the programme.

In eight cases with elevated AFP values both in serum and amniotic fluid, one spontaneous abortion occurred, three legal abortions were performed which yielded a normal fetus, and in four cases the pregnancy proceeded to term and a normal infant was born. During the period 1977–80 four to six cases of termination of pregnancy after the 18th week were reported in Sweden each year on the basis of elevated AFP values only.

As part of this project, a psychological evaluation[6] assessed the characteristics of the pregnant women who participated in the screening, and the psychological effect during the remainder of the pregnancy of the finding of an abnormal AFP value. It was demonstrated that receiving information about an elevated AFP value with a suspicion of fetal abnormality induced pronounced anxiety. For many women this reaction was long-lasting and in a few cases did not completely disappear until the baby was born. It was also concluded that there is a need for a qualified team of specially trained staff to handle the information and investigations in these cases in order to minimise the damage to the psychological balance of the mother.

Another conclusion of the study was that the upper normal limit for the AFP test could be raised and thus the need for additional investigations diminished, and that with the use of acetylcholinesterase determinations in amniotic fluid the problem of diagnosis of NTD in cases with an inconclusive ultrasound finding might diminish.

Acetylcholinesterase determination has been available in Sweden since 1985 and is now always done when raised AFP values are found in the amniotic fluid.

During the period of this collaborative project, AFP screening was introduced also in some other areas as a routine procedure in antenatal care and in 1980 approximately 20 per cent of the pregnancies in Sweden were tested. In succeeding years the screening was stopped in a number of counties. By 1985 less than 10 per cent of the pregnant population was offered AFP testing as a screening procedure, and in 1988 only three areas (6–7000 pregnancies per year together) still carried out this screening.

The AFP screening projects in Sweden thus resulted in an initial rapid diffusion of this technology, but as experience of the test increased, the participating doctors were increasingly negative to this form of screening. The reason for this was primarily the low specificity of the test, which resulted in a heavy workload for the doctors responsible (usually only one or two per county) and the close contact with the severe anxiety that was provoked by a usually false positive test in the pregnant women. Many doctors felt that the golden rule 'cause no harm' was broken by this procedure, especially as the information to the patient before the test was often not very detailed about the possible consequences. Also, the cases where abortion yielded an apparently normal fetus gave great concern.

With AFP screening fetal diagnosis became an issue for all pregnant women and this actually started the media debate on prenatal diagnosis (see later). AFP screening has remained the form of prenatal diagnosis most severely criticised in the media. The most frequent criticism attacked the fact that the test was used routinely and proposed by the antenatal care staff, which would easily give the woman the impression that the test was a necessary part of pregnancy surveillance.

After the screening had been stopped, there were no reports of any general reaction from the consumers. Some mothers who had been tested in a previous pregnancy asked for it, but when told that 'it is not routine any more but may be done if requested', they often did not do so.

The AFP projects were funded by the Swedish MRC and other research funds. The AFP test kit was marketed by a Swedish reagent company (Pharmacia), which gave financial support to information booklets and the printing of reports, both of which contributed to the spread of the test procedure.

The fact that *low* AFP values may indicate an increased risk for Down's syndrome has not yet been applied in clinical practice in Sweden, but there is a possibility that this will renew interest in general screening. From previous experience, however, a well-documented clinical trial to demonstrate benefits will probably be demanded before general screening is accepted.

Ultrasound for routine use in monitoring pregnancy was first introduced at the Department of Obstetrics and Gynaecology in Malmö and from 1975 all pregnant women in Malmö were offered two routine examinations at week 17–19 and week 33. The experiences from this programme have been reported.[7] The gynaecologist building up the ultrasound laboratory in Malmö, P-H Persson, has been a key figure in the introduction and training in ultrasound for routine obstetric use in Sweden. The department in Malmö has been a centre for research and training of both doctors and midwives and the programme and standards developed there have spread to the rest of the country.

The use of ultrasound in obstetrics slowly increased during the period 1975–80. By 1980 all university departments of Obstetrics and Gynaecology had access to the technology, and in three of them it was used for routine examinations in early pregnancy. In 1983 136,000 examinations were performed during pregnancy in Sweden (94,000 deliveries). In 1985, when the MRC arranged a state-of-the-art conference on obstetric ultrasound,

more than 60 per cent of the pregnant women in Sweden were reported to be included in an ultrasound screening programme with at least one examination, and a recent estimate claims that this figure is now 80–85 per cent. Statistics from three university departments show that screening in early pregnancy accounts for about 40 per cent of the total number of obstetric ultrasound examinations and that the main number of examinations per pregnancy is about 2.5. This development has occurred in spite of the fact that the conference made no recommendation in favour of general screening in normal pregnancy. A randomised study to evaluate the benefits of routine ultrasound screening has recently been performed in three hospitals but the analysis of the results is incomplete.

The routine programmes were introduced in order to detect fetal growth retardation, not fetal malformation, but with the increasing experience and improved technology it proved possible to detect gross malformations before week 20 in 0.5 per cent of the pregnancies within the screening programme. In no department in Sweden, however, is screening for fetal malformation at present presented as a main goal for examinations in the second trimester. In two centres the ultrasound examination is combined with AFP testing. It is reported that this decreases the danger of misinterpretation of the test and gives an immediate diagnosis of many cases of anencephaly and other gross malformations that may cause elevated AFP values.

Research on prenatal screening

Aspects of prenatal diagnosis have been the subject of quite a few dissertation projects in Sweden during the last ten years. The two projects on AFP screening[8,9] as well as the thesis on the psychological consequences of screening six have already been mentioned. In 1985 another thesis[10] investigated the psychological reaction of women who had a fetal defect diagnosed by ultrasonography in the second or third trimester. Substantial long-lasting problems were reported in the women who had had their pregnancies terminated because of fetal malformation. Also the severe stress reaction during the rest of pregnancy in the women who had had a late diagnosis was documented. In a recent project in Stockholm[11,12] the attitudes of women who have had CVS or amniocentesis and of their partners to the procedure itself, to handicaps and to the possibility of abortion because of the sex of the fetus have been investigated.

Legal abortions and prenatal screening

In the very first abortion law in Sweden in 1938 a eugenic indication for abortion was included. It was stated that abortion might be performed if the child had an increased risk of hereditary disease. In 1963, the so-called 'fifth indication' was approved, legalising abortion when the fetus may have a severe disease or handicap. Under the present abortion law, approved in 1974, abortion is available on the pregnant woman's decision up to 18 weeks of pregnancy. Thereafter abortion may be allowed until there is a possibility

of neonatal survival (in present practice 22 weeks) if 'exceptional reasons' can be adduced and after approval of a special NBHW committee. A diagnosis of fetal malformation or disease has so far always been judged as an 'exceptional reason', but it has been debated whether eg sex chromosome anomalies should be approved as justifying late abortion.

Thus, the abortions performed after 18 weeks for fetal malformation are reported but before 18 weeks no report of the reason for abortion is necessary. The number of late terminations because of fetal abnormality has increased from 34 in 1977 to about 100 per year recently. About 40 per cent of these cases were for Down's syndrome and 15 per cent for NTD.

It is at present being debated whether the present law is satisfactory with respect to the upper time limit for legal termination of pregnancy. It is argued that rapid progress in intensive care for premature babies makes it necessary to have a time limit for abortion that is more clearly separated from the period of gestation after which survival is possible. A government committee is now discussing this issue. A change of the abortion law on this point may well affect the gestational age at which prenatal diagnosis is performed.

Patients who are not Swedish citizens or permanently living in the country are not accepted for abortion unless there are special reasons.

INFLUENCES ON THE DIFFUSION PROCESS

Central government, the political parties and the central administration have so far played a limited role in the introduction of technologies for prenatal screening.

A government committee, the Gene Ethics Committee, presented its report[13] in 1984, including the issue of DNA-based prenatal diagnosis. It proposed that such diagnosis be restricted to severe genetic diseases that threaten the development of the fetus or the child. No general prenatal screening with these methods is proposed or discussed at present.

Since no changes of laws or regulations have been necessary for the implementation of screening programmes in prenatal diagnosis, it was actually the increasing awareness of the ethical problems, prompted both by public debate and questions from members of parliament, that in 1984 induced the permanent Parliamentary Committee for Health and Social Issues to commission the (government-appointed) Insemination Committee to describe the principal problems of prenatal diagnosis. The report[14] was released in 1989 and is currently being submitted to the usual consultation process by various organisations. It, together with the comments, is expected to form the basis of a governmental proposal on the issue.

The Committee report repeats earlier discussions on the differing interests of the fetus and the pregnant woman, concluding that selective abortion should be accepted in the mother's interests, although it is also stated that the fetus must be treated as having human rights. The question of each woman's right to demand prenatal diagnosis for a certain condition is not clearly answered: it is stated that the woman herself should decide, but that the examinations should be seen as medical interventions, with a doctor as the final decision-maker. No clear stand is taken on the very much debated issue of which kinds of handicaps should be subject to active prenatal diagnosis,

and which should be accepted as a reason for abortion. Generally, the report has carefully avoided the central question of the conflict between a liberal attitude towards the individual's wish to control his or her family and the wish to uphold certain value standards within society, eg with respect to equality between sexes.

The 25 county councils in Sweden have economic responsibility for all aspects of health care and decide on the level of a special county tax which covers all health care costs. However, the quality and standard of care is largely determined by the *National Board of Health and Welfare (NBHW)* in statements of what is considered good practice in diagnosis and treatment. Usually, after an issue has been debated in parliament, NBHW is required to write detailed regulations to be followed by the health professionals.

For prenatal diagnosis, however, this has not been the case. As mentioned above, NBHW appointed one expert committee in 1976 to advise on how to organise the genetic services. The expansion proposed at that time has been effected. The second expert committee in its first report[7] in 1983 presented current knowledge in prenatal diagnosis as well as psychological and ethical issues. In an appendix some questions were raised that were judged important for the handling of the technologies involved. The committee pointed out that the development of various technologies would gradually make possible an early diagnosis not only of severe fetal disease but also of minor deviations and defects. It would therefore be an unavoidable requirement for society to decide which diagnostic procedures should have priority, under what circumstances they should be performed, what information should be given to the parents about the fetus (especially when this had not been asked for) and what qualities in the fetus should be seen as sufficient reason to terminate the pregnancy. The question was also raised whether the decision about abortion should be the sole responsibility of the mother or whether it might be argued that special precautions would be necessary to prevent abortions in cases of minor or correctable disabilities.

The report was referred for evaluation to a number of administrative, legal, political, religious, professional and scientific organisations, and about 100 answers were collected. The great majority agreed that

a) the indications proposed by the committee were reasonable
b) a free choice for the woman to undertake prenatal diagnosis was essential but that she could not demand it
c) abortion should never be proposed or prevented against the woman's own wish within the time limits of the present abortion law
d) the problems produced by prenatal diagnosis must not lead to any changes of the abortion law
e) all information obtained must be given to the woman (possibly with the exception of fetal sex)
f) prenatal diagnosis should preferably be performed within the public health sector
g) general screening procedures (AFP screening often specified) should not be recommended
h) there was a need for guidelines on prenatal diagnosis.

A more restrictive view was advocated by the Christian churches, who rejected the idea of prenatal diagnosis as a quality control of the fetus and especially opposed all forms of general screening programmes. All abortions on this ground should be approved by the NBHW committee.

It is interesting that the organisations for handicapped and blind people, in their answer to the report, rejected absolutely the whole idea of prenatal diagnosis aimed at aborting a fetus with a defect. In contrast, the organisation in which also parents of handicapped children were represented accepted the idea of prenatal diagnosis as a service. This difference in attitudes between the handicapped and those who care for them is of course quite understandable.

Although it had been expected that, in accordance with usual practice, NBHW would proceed to work out general guidelines for the use of prenatal diagnosis, this task was given to the Insemination Committee. NBHW was asked to improve the care as well as the information given to pregnant women and their husbands both before they decided on prenatal diagnosis and after a result indicating a fetal defect. A booklet, *Information to Parents on Prenatal Diagnosis* was prepared and a one week course on the topic was given for the chief physicians responsible for the antenatal care in each county.

A revised version of the committee report 'Prenatal Diagnosis' was published in 1988,[15] but it does not attempt to propose regulations or guidelines.

The influence of *local county councils* on the diffusion of technologies for parental screening has been very limited in spite of their economic power. With few exceptions, there has been no active interest from the local politicians in furthering or hindering the development. In 1977 much attention was given in the media to a claim from the inhabitants in the northern part of Varmland county that more newborn children than expected had been seen with malformations, especially NTD. This was ascribed to the use of a certain plant poison applied to the forests in this area. The county politicians then advocated a programme of AFP screening as a means of detecting this type of fetal malformations. A subsequent NBHW-supported study failed to demonstrate any significantly increased incidence of malformations in the area.

In 1982, a Conservative county politician and economist in Stockholm carried out an economic evaluation of the prenatal screening programmes.[16] According to his calculations, the Swedish society would save 1250 million Skr a year in health care expenses by offering chromosome analysis to all pregnant women over 35 years as well as ultrasound screening combined with the AFP test to all pregnant women in week 17 (provided that the tests were accepted by the women and that a positive diagnosis resulted in abortion). The paper initiated a lively debate in the newspapers in which most of the participants, especially representatives from the handicap organisations, refused point-blank to accept economic considerations as a reason for prenatal screening. This debate no doubt strengthened the fears already expressed that there might be a real danger of prenatal screening being looked upon as a demand from society to minimise the costs of caring for the handicapped. Politicians from all parties, however, made general statements to the effect that no economic reasons should be allowed to determine the use of prenatal diagnosis.

The National Association of County Councils has taken a more active part in the last few years in stating priorities and taking central decisions on the use of the more expensive technologies. So far, there has been no attempt to discuss the use of prenatal diagnosis in this forum or to advise the counties on how resources should be allocated. Neither has the Swedish Institute for Testing and Rational Use of Health Care Technologies launched any study of prenatal diagnosis technology.

There is no doubt that a small group of *specialists in clinical genetics* have had a dominating influence on the introduction and diffusion of technology for prenatal diagnosis and screening in Sweden. They have not only introduced, adapted and developed the techniques, but have also been instrumental in informing and lecturing to medical professionals and to the public. They also give advice to individual patients or couples on the use of prenatal diagnosis. They have organised symposia and courses. They have participated in the general debate and been interviewed by the media when they present a new technique or when a media debate is flaring up. They are always represented in expert committees and they set the demands for resources needed. Three of the five leading clinical geneticists in Sweden are also specialised and highly qualified in important clinical fields (gynaecology, paediatrics and psychiatry), which increases their influence in the specialist organisations.

It should also be realised that the initial clinical research projects launched by the specialists and funded by research grants, especially if they are on a large scale, have the effect of increasing demand for the technology, also in routine care outside the project, even before the project is evaluated. The AFP projects illustrate this mechanism.

In general, doctors and health professionals working with rehabilitation of handicapped children have actively opposed prenatal diagnosis in the media debate.

With the exception of the organisations for handicapped people, no *individuals or groups of consumers* have come forward publicly to represent the general 'consumer interest', in this case the women of childbearing age or pregnant women. Even when there has been intense debate on ethical and other issues, few people have participated in order to give their personal view as parents. Those who have done so are mostly parents of a handicapped child, and have often not been in favour of encouraging the use of prenatal diagnosis to avoid the birth of a similar child.

Women's organisations have not been very active in the debate. Their most pronounced opinion has been to support strongly the autonomy of women with respect to every kind of abortion decision. This is one issue with no clear differences between the political parties, with the exception of the very small party of Christian Democrats. There is no clear 'feminist' standpoint on this issue although there have been some articles claiming that universal prenatal diagnosis is one step towards a total technological handling of the reproductive process.

On the other hand, individual patients or parents often have used considerable pressure on gynaecologists and laboratories in order to have a chromosome analysis or an ultrasound examination performed. This has naturally influenced the doctors involved to demand resources to cover at least the number of

prenatal examinations needed to meet the indications put forward in the NBHW report. As all care during pregnancy is completely free of charge in Sweden, there are no economic restrictions from the patient's point of view.

A few parents have tried to claim financial compensation from the county council for not having made prenatal diagnosis available during a pregnancy which yielded a handicapped child. None of the claims has succeeded, since the law states that individuals cannot demand any specific medical procedure if there are insufficient facilities or no medical indication.

Cytogenetic examinations are not undertaken privately, but ultrasound examinations have been undertaken in the rather small sector of private gynaecological practice during the last five years. In some cases, this has led to abuse , and a large number of examinations have had to be paid for by general health insurance. The *Swedish Association for Gynaecologists and Obstetricians* has warned its members against this practice.

This specialists' union is very active in organising postgraduate training in all areas of the speciality, and regular one week courses are given at university clinics. New technology is thereby quickly spread within the region. Initially, patients will be referred to the central hospital of the region, but as this procedure proves costly for the counties, their politicians will incline to building up local resources. This is also a means of increasing the prestige of the local hospital and making it more attractive to their specialists.

Courses in ultrasonography, both introductory and advanced, have also been organised for gynaecologists and are now considered mandatory for all gynaecologists in specialist training. Prenatal diagnosis is also included as a topic in all specialist courses in perinatal medicine or obstetrics.

The professional medical organisations also play a role through their ethics committees or delegations (one for the Swedish Medical Association and one for the Swedish Medical Society). In 1979 the Swedish Medical Society published the document 'Ethical Aspects of Prenatal Diagnosis'.[17] Both the fetus's right to life and the right of the woman to choose to have the test and to decide whether to terminate the pregnancy were emphasised. The ethical delegation also pointed out that further research could open up possibilities for treatment of fetal disorders and this might in fact increase respect for the rights of the individual fetus. The influence of this document has been considerable.

There is no doubt that the *individual attitudes of doctors*, especially gynaecologists in responsible positions, are important factors. The NBHW report 'Prenatal diagnosis'[3] reported the results of a questionnaire sent to all departments of obstetrics and gynaecology in Sweden asking how they informed women about the availability of chromosome analysis. Twenty out of 35 said they actively recommended the test when the mother was over 40, 33 would give information on the test to women of 35–40, two thought that information should be given to the women only on demand. A procedure recommended by the doctor will probably usually be accepted unless the woman is decidedly against it. The *Church of Sweden* and other religious bodies have in general had a positive attitude to prenatal diagnosis when some treatment is possible, but have been more doubtful when the intention is to abort fetuses with handicapping conditions. They have also been worried about the effect

of the general use of fetal diagnosis on the attitudes towards handicapped persons in society and upon the respect for human life and people's equal rights and value. An ecumenical group of experts was invited in 1979 by the Bishop's Conference of the Swedish Church to analyse the various aspects of prenatal diagnosis, and their report 'Fetus, Family, Society' (1980)[18] has been of great importance for formulating the problems associated with prenatal diagnosis.

For a long time the *media debate* was almost non-existent except for positive reports about new technologies and the possibilities they opened up to avoid the birth of children with handicap. Generally, prenatal diagnosis was presented as a method 'to avoid abortion of healthy fetuses' and thus the more questionable issue of selective abortion was put in the background. This issue was lost in the continuing debate on general abortion during the years before the abortion law was passed in 1974. Since then, there has more often been a conflict between those critical of prenatal diagnosis and those afraid of any attack on the right to free abortion.

It was only in 1978 that a doctor and two sociologists working in care of the mentally handicapped started a debate on prenatal diagnosis. In articles both in local and national newspapers they claimed that the main reason for the wish to avoid the birth of a handicapped child was the unwillingness of society to allocate enough resources to assist these children and their families. This provoked a general debate with participants from doctors, handicap associations, politicians and the general public. Public meetings were arranged in several places and suddenly firm opinions on prenatal diagnosis emerged. AFP screening programmes were especially criticised, and the right to a good life for the handicapped was stressed by both politicians and parents.

Despite this, the Association for Handicapped Persons claimed in their programme for 1977 that all pregnant women should be entitled to examinations that might give information about handicaps. The Association for the Mentally Handicapped stated in 1976 that the genetic service for the detection of fetal defects should be improved, but in 1979 several groups within the handicap associations made statements demanding an end to general prenatal screening. In contrast to more positive attitudes expressed earlier by parents' organisations, the Association for Parents of Mentally Handicapped Children took a firm stand in 1986 against all forms of prenatal diagnosis. It has been repeatedly claimed that only individuals who live with a handicap have the right to judge whether it really presents an unbearable degree of suffering.

Since 1978 the debate on prenatal diagnosis has never completely stopped, and periodically become more intense, eg when the reports from NBHW or the Gene Ethics Committee were published. A journalist, Sture Gustafsson, wrote three books during 1980–6 in which he summarised the different standpoints, generally advocating a critical and restrictive attitude.[19, 20, 21] In 1985 a TV film vividly illustrated the plight of parents awaiting the result of amniocentesis. Several TV programmes have also described positively the life and developmental possibilities for children with Down's syndrome and other handicaps.

Release of the new Committee report in 1989 has again intensified the ethical debate, the main antagonists being a lecturer in medical ethics arguing

a utilitarian – individualistic point of view, and a retired governmental official who has been successfully strengthening the social network of support for the (especially mentally) handicapped, arguing against a misdirected and prejudiced classification of individual lives.

There are no real signs that this ethical debate has influenced the allocation of resources for prenatal diagnosis or diminished the demand from individual parents. In fact, the lively debate during 1978–9 coincided with a significant increase in the number of prenatal chromosome diagnoses performed; no doubt the media attention served to increase awareness of this diagnostic possibility among parents. Probably the most pronounced effect of the general debate is that it has precluded the automatic inclusion of prenatal diagnosis as a more or less routine procedure in antenatal care. This has mainly affected the use of AFP as a screening procedure, but has not decreased the positive attitudes of parents towards ultrasound screening, which is generally not looked upon as a test for fetal defects but as an opportunity to get a more real experience of the expected child.

CONCLUSIONS AND ANALYSIS

Introduction of the various technologies for prenatal diagnosis in Sweden has been to a major extent governed by the specialists within the sectors concerned, of whom the specialists in clinical genetics have been most important.

Presentation of new techniques in the media was initially uniformly positive to this means of avoiding the birth of a child with a handicap. No general debate on the advantages and problems of the technology began until it was well established, and a general consumer interest has at no time been clearly documented either politically or in the media. Individually, however, many consumers have exerted considerable pressure to have certain diagnostic procedures performed.

Attempts to introduce the economic argument of saving the costs of care for the handicapped as a reason for prenatal diagnosis have met with very negative reactions and there is consensus that the wish of parents to avoid the personal tragedy of giving birth to a child with a severe handicap is the only valid reason for undertaking the procedure.

The introduction of a general screening programme (AFP) opened up media discussion about the ethical problems of prenatal diagnosis, and this debate has continued since. However, this does not seem to have slowed down a rapid increase in the uptake of prenatal diagnosis, with the exception of AFP screening. The main reason for the low use of AFP testing, however, is not to be found in a general resistance among consumers but in negative experiences among most doctors of the psychological problems associated with general AFP screening in a low-risk population.

The use of serum AFP measurements for general screening may possibly be resumed now that it may be a means of detecting pregnancies with increased risk of Down's syndrome.

The demand for chromosomal analysis seems to have levelled out at about 5 per cent of the pregnant population; there is a definite trend towards increased use of CVS instead of amniocentesis.

Although some form of prenatal diagnosis is now mooted as part of antenatal care for almost every pregnant woman, no central decisions have been taken either on its appropriateness or on the size of the resources that should be allocated. The difficult ethical problems associated with prenatal diagnosis may have made politicians and administrators hesitate to take a clear stand on a controversial issue. It seems that the rules and regulations in this area now increasingly being demanded from politicians are more attributable to the fear that in the future genetic and morphologic diagnosis will also be able to detect minor deviations from the norm than to a wish to restrict the present use of prenatal technology.

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DIFFUSION OF PRENATAL SCREENING IN GREECE

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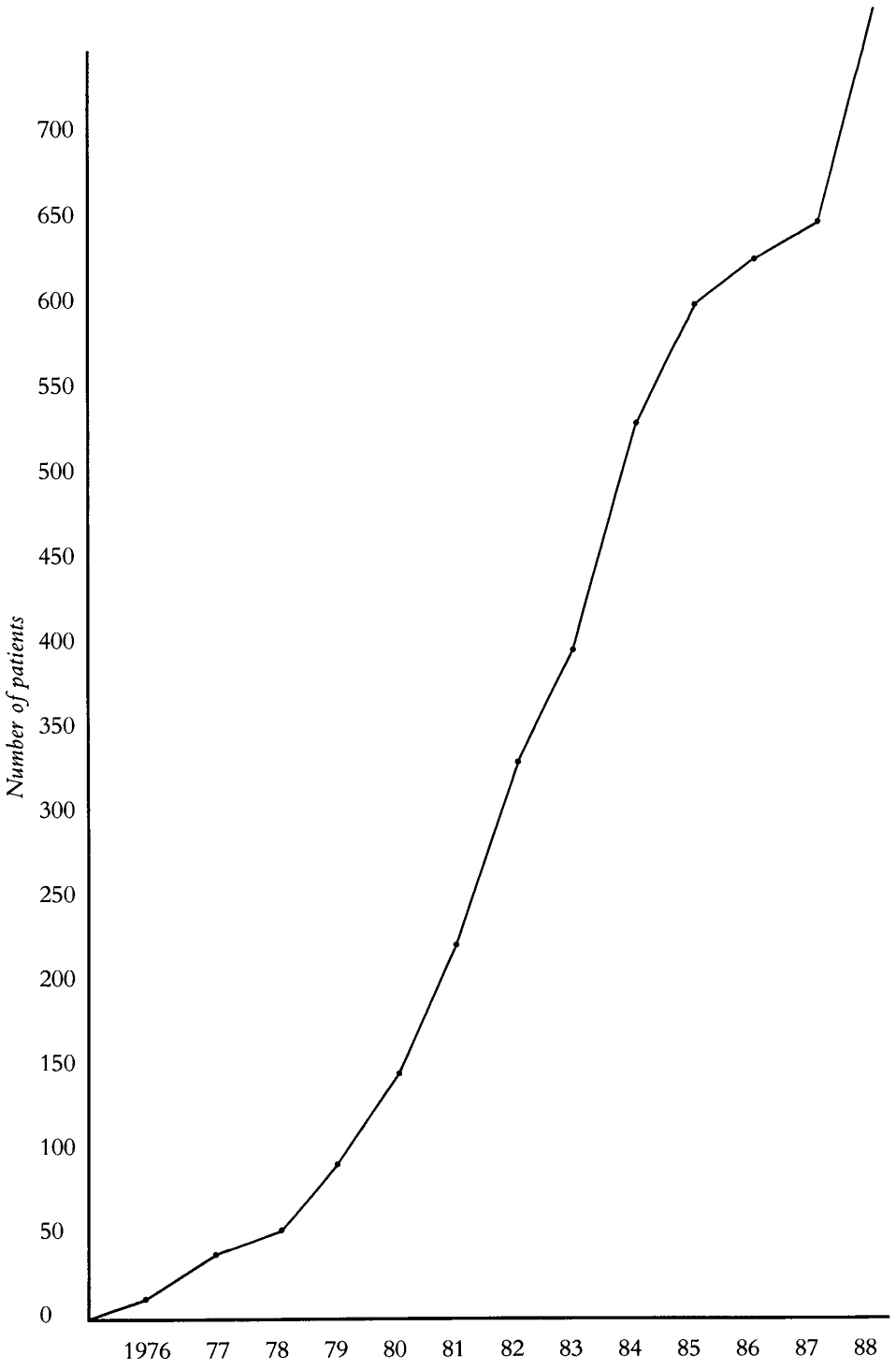
Prenatal diagnosis for chromosomal abnormalities after second trimester amniocentesis was initiated in Greece in 1976. In the first year only six cases were tested, because of the negative attitude of the professionals and public anxiety about amniocentesis. After Parliament changed the abortion law in 1977, following a major round-table discussion in which representatives of the Greek Orthodox church and the medical and legal professions participated, the demand for prenatal diagnosis increased, leading to 220 cases in 1981. Since then the number of pregnancies investigated annually has increased rapidly.

Until 1981 there was only one genetics centre, the Genetic Unit of the 1st Department of Paediatrics of Athens University, where prenatal diagnosis for chromosomal abnormalities was performed. Cases were referred mainly from the Obstetrics and Gynaecology Department of Athens University at Alexandra Maternity Hospital and from a few other obstetricians. In 1981 the state established a second genetics centre for prenatal diagnosis at the the same hospital and in 1984 a third genetics centre was created in Thessaloniki. Since 1986 some private laboratories also exist in Athens and Thessaloniki. Figure 1 shows the number of cases investigated per year at the genetics centre of the 1st Department of Paediatrics, which covers approximately half of the prenatal diagnosis tests performed in Greece. An increasing rate of requests is also observed at the other genetics centres.

From the beginning the Ministry of Health supported the establishment of prenatal diagnosis centres, by providing funds for the purchase of the necessary equipment and the hiring of personnel and by establishing the genetics centre at Alexandra Maternal Hospital. Prenatal diagnosis, however, was initiated and developed at the university medical schools of Athens and, later, Thessaloniki.

The public was informed mainly through the medical profession, in scientific meetings, by increasing the awareness of professionals in medical technology. The public was also informed through the mass media. The process was facilitated by the fact that the establishment of a prenatal diagnosis centre for chromosomal abnormalities was paralleled by one for thalassaemia, which was also advertised to the public. Prenatal diagnosis for haemoglobinopathies was performed at the Department of Internal Medicine of Athens University in collaboration with the obstetrics department where sampling was performed. At the same time (1977), Greek legislation was changed to allow termination of the pregnancy for medical reasons up to the 24th week.

Figure 1 *Number of cases investigated per year in 1976–88 at the Genetic Centre of the 1st Department of Paediatrics, Athens University*



FACTORS AFFECTING THE DIFFUSION

Availability of amniocentesis

For the first three years, all the amniotic fluids referred to the Athens laboratory came from a limited number of obstetricians who performed the amniocentesis themselves. As time passed, other obstetricians became aware of the technology through presentations at scientific meetings by staff of the Athens University department and the Alexandra Maternity Hospital. Younger obstetricians learned the technique during their training, and those who were trained also spread the word around. Thus the number of obstetricians who could perform amniocentesis increased.

Availability of genetics services

Requests for amniocentesis are unequally distributed across the country. Although only 31 per cent of the 25- to 55-year-old Greek population live in Athens and Piraeus, over 63 per cent of the referred cases come from the greater Athens area. We believe that this is mainly because the population around Athens is more aware of the availability of prenatal diagnosis; also, it is easier for women living near Athens to reach one of the prenatal diagnosis centres. Transport difficulties could be the reason for the limited member of requests from the islands.

The relatively small number of amniocenteses in Northern Greece is probably due to the fact that the genetics centre of the University of Thessaloniki began operations only in 1984 and still has limited capacity. There is in addition a private laboratory which sends the amniotic fluid samples abroad.

Educational level of parents

Table 1 shows the educational level of the Greek couples requesting amniocentesis at the Athens centre in 1987, and the educational level of the Greek population aged 25–55. In 25 per cent of the couples requesting amniocentesis one of the two partners had a university degree, when in only 10 per cent of Greek couples one of the two partners holds such a degree. It is easy to understand why the better educated individuals are more aware of the potential of prenatal diagnosis.

Table 1
Educational level of couples requesting amniocentesis compared with that of Greek couples in general 1987

	Requesting amniocentesis	Population 25–55 yr
Up to 6 years' education	22%	34%
High school education	40%	47%
Higher technical education	6%	9%
University level	25.5%	10%
No information	5.5%	–

Although the figures are not entirely reliable they reflect the general picture. There are no genetic counselling clinics in the Greek provinces. In our experience, most cases are referred from gynaecologists and obstetricians around the country, and the uptake of prenatal diagnosis in the various areas of Greece depends mainly on how well informed the local obstetricians are. Young obstetricians are in general well informed, follow the scientific literature and attend scientific meetings regularly, even if they work outside Athens. Older ones tend to continue their private practice in traditional ways and to resist change.

INDICATIONS FOR PRENATAL DIAGNOSIS

The main reason (55 per cent of requests) for requesting prenatal diagnosis during the early years (1976–7) was the anxiety caused by a previous child with Down's syndrome; later, this reason was overtaken by maternal age, which reached 90 per cent by 1988. Thus the public has become aware of the benefits of prenatal diagnosis, and the group at high risk of chromosomal abnormalities is being investigated. We calculate that the potential demand for prenatal diagnosis in Greece is about 5000 cases if the lower limit for maternal age is set at 35 and 3000 cases if it is 37.

At present the limited resources are causing great difficulties in servicing all the referred cases. The genetics unit of the 1st Department of Paediatrics of Athens University performed 650 tests in 1987 and 950 in 1988; a further 537 pregnancies were tested in two other national health genetics centres and 300 by a private laboratory.

Of the 5115 cases examined in Athens since 1976, 82 abnormal embryos have been identified. As there are no reliable data for the incidence of stillbirths or children born with multiple congenital anomalies in Greece, we cannot estimate whether the use of prenatal diagnosis has effectively reduced the birthrate of children with chromosomal abnormalities. On the other hand, knowing the psychology of the Greek people we can state with certainty that prenatal diagnosis in Greece has made this contribution: families who have had a child with a chromosomal or other congenital abnormality now dare to have another baby, given the reassurance of prenatal diagnosis. The main problem currently is meeting demand.

TECHNIQUES OTHER THAN CHROMOSOMAL ANALYSIS

Because the incidence of open neural tube defects in Greece is low (only 1.45 per thousand births) there has been an explicit decision not to mount a national programme of maternal serum AFP screening. AFP is, however, measured in all the amniotic fluids sent to our laboratory for chromosomal analysis and in the amniotic fluid from pregnancies where ultrasonography suggests an open neural tube defect.

In Greece there are numerous private centres for ultrasound scanning, and a large number of pregnant women living in the urban areas have at least one ultrasound scan during their pregnancy. It is not possible to estimate the extent to which this technology is used.

Since 1983 the laboratory of the 1st Department of Paediatrics has also performed CVS for prenatal diagnosis of cytogenetic abnormalities in the first trimester of pregnancy. Table 2 shows our experience with CVS since 1984. The women tested in our series by CVS were not randomly selected. Our impression is that in Greece a randomised study of CVS will not be easy, since women wish to choose the method of prenatal diagnosis.

Table 2
Pregnancies tested for fetal karyotype by CVS, 1984–8

Reason for referral	No.	Successful karyotyping	Abnormal embryos
Maternal age >35	273	252	13
Previous abnormal child	58	52	–
Parental translocation	6	6	–
Other	18	17	2
Total	355	327	15

This table does not include karyotyping for X-linked disease.

First-trimester prenatal diagnosis is rapidly being accepted, and although some technical difficulties are still unsolved it appears that in future, CVS in experienced hands will be the method of choice for chromosomal abnormalities. First-trimester prenatal diagnosis is also performed in a private laboratory in Athens.

Since 1985 amniocenteses have been performed in all the maternity hospitals of the country, State and private. The difficulty however arises from the fact that there are still very few laboratories where the fluids are sent for testing. This creates a tremendous burden for the existing genetics centres, and emphasises the importance of establishing additional ones. Further laboratories have been proposed in Patras, Heraklion, Ioannina and two other cities, but they have not received State funding.

DIFFUSION OF PRENATAL SCREENING IN PORTUGAL

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THE HEALTH CARE SYSTEM IN PORTUGAL

Portugal has about 10 million inhabitants. The birthrate has been declining in the past few years, from 123,416 total births in 1987 to 98,545 in 1988.

Prenatal care is included in the National Health Service and is delivered at two levels: as part of primary health care, provided by general practitioners in health centres located at community level; and in obstetric units in general or maternity hospitals, usually located in major cities, where high-risk pregnancies can be referred.

Pregnancy surveillance includes screening for rubella, toxoplasmosis and syphilis. Ultrasound examinations are routinely performed in almost all pregnancies.

Primary health care units and hospitals belong to and are supported by the State, but any doctor can also have a private practice, and many women, even in the countryside, prefer this kind of surveillance. The relative proportions of these two types of surveillance is not known.

There has been no official policy until now on screening for congenital anomalies such as neural tube defects (NTD) or Down's syndrome in mothers above a certain age. Maternal serum alpha-fetoprotein is not measured routinely, and prenatal diagnostic facilities are in short supply.

Of the 123,416 births in 1987, 36 per cent occurred in Lisbon and Oporto, and 9 per cent were to mothers over 35 years of age. Only these two cities have prenatal diagnosis facilities; the greatest distance to a town from Lisbon southwards is 299 km (Faro) and the greatest distance from Oporto to the north is 253 km (Bragança).

INTRODUCTION OF THE TECHNOLOGIES TO PORTUGAL

Prenatal screening technologies were introduced into Portugal in the early 1970s, first as an experiment and later as a selective offer to some women. It appears that these moves were the result of pressure from academic medical research workers.

The pioneer in Portugal was A Tavares, Professor of Genetics in the University of Oporto. His team introduced cytogenetic analysis of amniotic fluid cells in 1972. At first the aim was purely informative, in response to the request of parents who wished to know whether they could expect a normal neonate. Selective abortion was not considered. Actually, doctors thought at the time that termination of pregnancy was not their business.

As time passed another laboratory, this time in Lisbon at the National Institute of Health, introduced the same techniques. This laboratory, run by non-medical geneticists, received amniotic fluids from obstetricians and

disclosed information to the patients if the result was normal, or to referring physicians otherwise. There was no prior genetic counselling and the problem of termination was entirely in the hands of the referring obstetricians, who might agree with it or not.

In the mid-1970s important political events shifted Portugal towards democracy. A much freer society emerged, with freedom of opinion and of the Press. These events can be related to a rise in the demand for prenatal diagnosis, especially from women who had been informed by others or by the Press.

It was not until 1985, however, that another centre appeared in Oporto, at the Institute of Medical Genetics, this time with a definite commitment to support the patient right through to a termination of pregnancy if that was considered necessary.

In 1988, the Service of Medical Genetics in Lisbon (Hospital de Egas Moniz), began to offer a service. The patient is referred by a physician and first receives genetic counselling. The indicators, risks and issues are discussed with the couple, and amniocentesis is performed by the same obstetrician who is responsible for the termination when necessary.

These four centres operate in the two main cities of the country: Lisbon and Oporto. This is obviously related to the location of large hospitals and universities in these cities. In these places, individuals or groups had both motive and opportunity to introduce new technologies.

Professional interests within the medical profession or other health care professions were in advance of Government policy concerning the inclusion of these technologies in the National Health Service; and also, it appears with hindsight, in advance of consumers' demands.

DEVELOPMENT: VARIOUS INFLUENCES

Genetic services

The four centres described above had the advantage of starting the new technologies themselves and it was in their own professional interest to offer them to the community. Their work has been hampered by shortage of funds, understaffed teams and lack of sufficient equipment. Despite subsequent expansion of these services, only a minority of women in the high-risk group (›35 years) benefit from prenatal diagnosis for Down's syndrome. The number of analyses done was small compared with the size of the high-risk group. For example, the two services in Oporto made not more than 200 investigations for Down's syndrome during 1988 (about one-fifth of those eligible). Demand is now rising and will soon outstrip by far the service capacity.

Members of the medical profession

Most general practitioners and other physicians, particularly the older ones, are not well informed as to the benefits and exact indications for prenatal diagnosis.

Some obstetricians are well informed and willing to cooperate in obtaining samples for analysis, but do not wish to be involved in termination of pregnancy. Only a few are well informed, have the experience and skill to obtain samples, and commit themselves to terminating selected pregnancies. However, even these must still submit to the opinion of an Ethics Committee which some Obstetrics Units have recently set up.

Doctors and nurses are allowed to be conscientious objectors to termination of pregnancy. If the Head of an Obstetric Unit is such an objector he or she may prevent termination from taking place in the Unit. But even where terminations are allowed to take place, any doctor or nurse may refuse to take part.

Consumers' views

Many women at risk, particularly those living in the countryside, are ill-informed about prenatal diagnosis. Information is difficult to obtain if they cannot get it from their doctor; and travelling to the main centres can be difficult and expensive.

After the political changes of the mid-1970s, the public became increasingly aware of the advantages of prenatal diagnosis. Women start demanding information and screening from general practitioners and obstetricians. When they do this, there are three possibilities:

a) the doctor objects to prenatal diagnosis because of the possibility of termination of the pregnancy, and refuses to collaborate;
b) the doctor accepts prenatal diagnosis, informs his or her patients and sends them to the appropriate centres, but will not be committed to the possibility of termination;
c) the doctor fully informs his or her patients, takes part in obtaining samples and commits him or herself to the end.

In a study of how much patients know about the benefits and risks of prenatal diagnosis, all women attending the Prenatal Clinic of the Medical Genetics Service (Hospital de Egas Moniz) had a counselling session prior to amniocentesis. All had been referred by an obstetrician or general practitioner. Results from the interviews included the following:

a) of the 85 women referred, 69 accepted prenatal diagnosis and 15 declined it after being given the requisite information
b) 63.8 per cent of the women knew nothing of prenatal diagnosis; 31.8 per cent knew a little, but far from sufficient; 4.4 per cent had 'enough information'
c) among those who knew anything, this had been given by doctors, the press or friends
d) in answer to 'What is your religion?', 73.5 per cent declared themselves Catholic, 3.1 per cent had another religion and 23.4 per cent said they had no religion. No member of the Catholic group thought that acceptance of prenatal diagnosis and abortion because of fetal anomalies had anything to do with religious beliefs.

e) Of the 15 that declined the service, the reasons were: no actual indication, 8; no explanation, 2; arrived late in pregnancy, 3; no feasible test for their condition, 2.

Law and Government

There is no official policy of screening for congenital anomalies, so that we cannot speak of a prenatal screening service at national level. However, a working group has now been appointed by the Ministry of Health, with a remit to study the development of Medical Genetics Services.

Parliament has recently passed two laws which are relevant.

Law 4/84, Protection of Maternity and Paternity, establishes that prospective parents are entitled to free medical examinations and all laboratory analyses considered necessary by their doctors, during pregnancy and for two months after delivery.

Law 6/84 precludes legal punishment in certain cases of abortion, namely congenital anomalies or severe disease of the fetus. Termination is allowed up to the 16th week of gestation. Doctors and nurses retain the right to be conscientious objectors.

THE CATHOLIC CHURCH

The Catholic church is an important influence in Portugal. Its influence must be taken into account in ways of thought, attitudes and behaviour in general but especially of many members of the medical profession who refuse to accept prenatal diagnosis if it entails abortion. The Catholic church openly takes a position against abortion in general and makes no distinction in favour of termination because of severe fetal disorder.

The Association of Catholic Doctors opposes prenatal diagnosis if a termination is to be considered as a result, but they consider it a duty to provide all information sought by their patients.

PUBLIC DEBATE

To date there has been no major public debate on the philosophy, techniques and issues in prenatal diagnosis. The mass media have from time to time approached this topic, usually at the instigation of genetics services seeking public support and Government attention and funds, but without much impact.

FACTORS AFFECTING THE DIFFUSION OF THREE KINDS OF INNOVATIVE MEDICAL TECHNOLOGY IN EUROPEAN COMMUNITY COUNTRIES AND SWEDEN

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CONTENTS

1 INTRODUCTION

The three technologies whose diffusion is considered in this study are very different in nature.

One, lithotripsy, involves heavy capital investment in a single piece of equipment which can serve a large population; another, heart transplantation, requires considerable surgical and scientific skills, sophisticated information and transport arrangements, and resolution of ethical issues, but no massive new equipment; and the third, prenatal screening, requires relatively simple procedures but a well-organised infrastructure of specialised centres liaising with obstetricians, as well as another kind of ethical consideration which demands the sympathetic consensus of religious bodies, the public and State laws.

By taking three rather different technologies we hoped to identify the similarities and differences in their uptake and use. Box 1 defines the technologies in more detail.

BOX 1

Prenatal Screening

Four tests were considered under this head, two of which are in fact diagnostic rather than screening (amniocentesis and chorionic villus sampling), one which can be used for both screening and diagnostic purposes (ultrasonography), and one which is truly a screening procedure, maternal serum alpha-fetoprotein assay.

The four tests are:

amniocentesis: a procedure usually performed at around 17 weeks of pregnancy, in which a small quantity of the amniotic fluid surrounding the fetus is withdrawn through a needle inserted through the abdomen and uterine wall. The fluid and the fetal cells it contains may be tested by chromosomal analysis for different disorders in the fetus.

chorionic villus sampling (CVS): a procedure by which a small quantity of the chorionic villi on the surface of the placenta is withdrawn for DNA analysis. CVS can be performed at any stage of pregnancy from about 8 weeks of gestation.

maternal serum alpha-fetoprotein (MS-AFP) screening: AFP is a protein derived from the fetus, present in the amniotic fluid and also circulating in traces in the maternal bloodstream. The concentration of AFP in maternal blood serum can be used to screen for neural tube defects in the fetus and, it has been claimed more recently, for Down's syndrome too.

ultrasonography: a process using high-frequency low-energy sound waves that can be focused and used to produce images of tissues, organs or structures within the body. Physical malformations can be detected with greater or lesser certainty depending on the quality of the equipment and skill of the operator. Periodic ultrasonography can detect fetal growth retardation.

BOX 1 continued

Stone Treatment
Kidney stones were traditionally removed using open surgery. In the 1970s two alternative technologies were developed: extracorporeal shock wave lithotripsy (ESWL) and percutaneous nephrolithotomy (PCN).

Lithotripsy uses a source of shock waves outside the body. These waves are focused on the stone and cause it to disintegrate. The particles are then passed out through the body in urine.

PCN involves endoscopic removal of stones. Direct access to the stone(s) is made through surgical incision into the body. Miniaturised endoscopic equipment is used to locate and remove the stone.

Endoscopic treatment and the use of lithotripters are also being developed for gallstones.

Organ Procurement and Transplantation
Both these terms are self-explanatory, but it should be noted that the study focused particularly on heart and liver transplantation, with some reference to the earlier introduction of kidney transplantation.

The second strand to the analysis concerned comparison among the EC community countries and Sweden. Among them these countries have a considerable range of cultural diversity as well as various types of health systems, and it was important to discover whether this resulted in differences in how new medical technologies are introduced and spread. A previous study[1] looked at the formal regulatory processes, but policy makers and individuals within health systems recognise that these are only one of the influences on the diffusion process. We were interested in learning whether the influence exerted by the various actors involved in the diffusion process was similar across the different health systems and regulatory mechanisms, and whether different factors were important in different countries.

If governments are serious about controlling and deploying their health expenditure to best effect, one recommendation emerges very clearly from this study. They need to improve their data collection about the existence and use of medical technologies. We expected from the start that country rapporteurs would have to seek hard for evidence about what influenced the diffusion of technologies, but it was surprising how much difficulty rapporteurs had in obtaining straightforward facts such as the number of items of equipment or procedures undertaken. When the technology involved large, expensive items of equipment like the lithotripter, the data were somewhat more readily available. It was less easy for procedures such as amniocentesis. However, even with lithotripsy there is a need to know how many stone treatments were performed prior to its introduction and how many open or

endourological procedures take place now. Both pieces of information are in very short supply, if not unobtainable.

Some countries have better data than others. It might be expected that nationalised health systems would have uniform full-coverage data. However, this was not the case for the three technologies in this study. On the contrary, countries where reimbursement mechanisms are used may in fact have better information, especially on procedures. On the whole though, central records on the technologies and procedures were not generally available and each technology required considerable investigation. Transplantation data were the most readily available because of the national and international networks for organ matching that are in operation (e.g. Eurotransplant and Scandia Transplant).

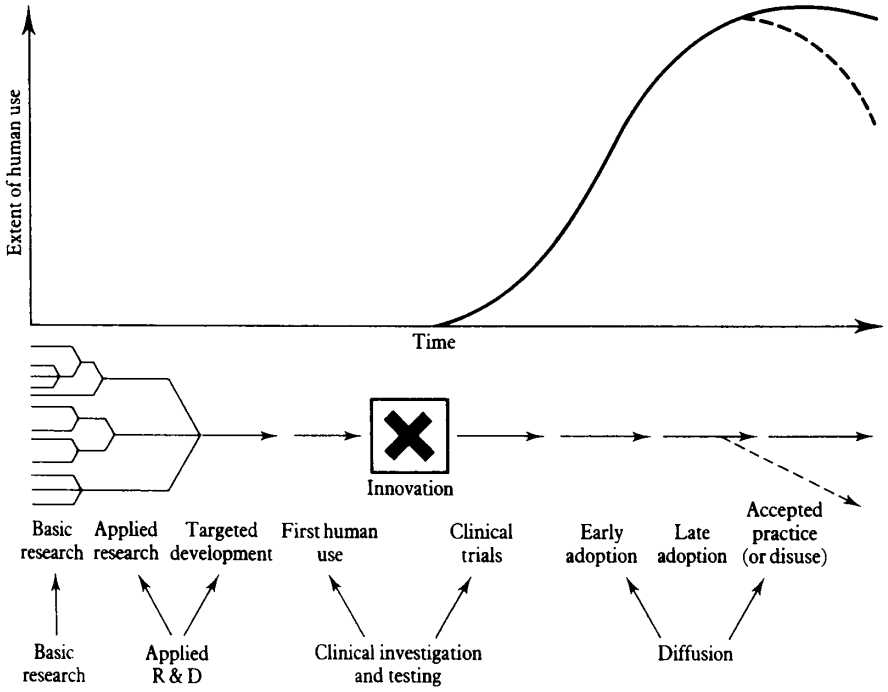
In this overview the introduction and diffusion of the three technologies are examined and then the factors which influenced the speed and extent of this diffusion – this includes the nature of the technologies themselves, social and economic characteristics of the countries, and finally the more specific influences on their diffusion. Some surprisingly clear patterns emerge which do lead to a common agenda across Europe even if this needs to be implemented in country-specific ways.

2 THE DIFFUSION OF THREE MEDICAL TECHNOLOGIES IN EC COUNTRIES AND SWEDEN

The diffusion process

Many people do not realise that there is a common pattern to the way new ideas diffuse.[2] Medical technologies fit this overall pattern, illustrated in Figure 1.

Figure 1
Stages in the development and diffusion of medical technologies



First the innovation has to be developed; it may go through a number of false starts before it reaches a definable product, regardless of whether it is a clinical procedure or a product which can be sold on the market, such as drugs or equipment.

Once the innovation is in prototype form it has to be adopted by some of the key people in the relevant professional or societal group. It is then that there are sometimes differences between medical equipment and procedures. Equipment developed in industrial laboratories will have to be tested out in clinical settings, so that relevant clinical departments may have to be persuaded of the innovation's potential usefulness. This will be less of an issue if the basic ideas were developed in a hospital or university research laboratory, or if there have been links between industry and the health system throughout.

Clinical procedures will have been developed by clinicians themselves, though perhaps in collaboration with others.

The first people to try something are often seen as mavericks and it is only when respected opinion leaders begin to take up the technology that more general acceptance becomes possible. There are inevitably a few 'laggards' who may never accept the idea.

Of course, this overall pattern tells us little about the time scales involved, the rate of adoption, or the ultimate saturation point. For example, for a number of expensive technologies saturation is likely to mean that all the specialist centres have taken them up, not that every hospital in the country has the technology. Also, some technologies may be starting to diffuse when they are superseded in whole or in part. Other factors may intervene, such as a change in government policy or in reimbursement criteria. So the diffusion curve provides the underlying skeleton, but there is much more to understand about what actually takes place.

Perhaps the most interesting difference of medical technology from the diffusion of innovations described in the classic literature is that the adopters are often not individuals who can independently decide to adopt or reject, but are part of large complex systems. The innovation itself may require the commitment of a number of people from different professional backgrounds. The negotiations required for acceptance are at least as interesting as the speed and extent of diffusion – hence the analysis undertaken in this study.

Innovation development

The developmental histories of the three technologies in this study provide a rich account of the trials and tribulations of innovation development. New medical technologies do not suddenly appear from nowhere. A number of scientific breakthroughs is often required, sometimes from quite different fields. Organ transplantation illustrates the length of time innovations may take. It was more than 50 years before animal experimentation on kidney transplantation in 1901 led to clinical reality in humans. There were technical surgical issues to be overcome, but the real key to success was the understanding of the immune system and the development of drugs to suppress the immune reactions to the transplanted organ. The first successful transplants using genetically related donors took place in 1954 in the US and UK. Diffusion really only got started after the first successful kidney transplant using a cadaveric donor in 1962 and after the development of matching for histo-compatibility. When immunosuppression made non-related donor transplantation much more successful there were teams in readiness in a number of countries skilled in using living related donors for transplantation. Thus, the essential infrastructure for the innovation to diffuse was in place in skeletal form.

Heart transplantation in humans began rather later, but had a false start. The first transplant was done in South Africa by Dr Barnard in 1967. To reach that point a number of breakthroughs were required including, in 1953, the development of the extracorporeal circulation pump. What had not been overcome though in 1967 was the rejection problem. Although a number of countries then began transplantation, by 1970 all but five centres had stopped. In

Stanford, USA, the work continued, but it took a further ten years for survival results to improve significantly. By that time cyclosporin had become available. It was first tested in clinical transplantation by Calne in the UK, in kidney transplantation in 1978, and shortly afterwards heart transplantation started in earnest. Liver transplantation also had to await cyclosporin before taking off. However, as shown below, its diffusion is still considerably slower than with heart transplantation.

Prenatal screening development was also a slow process but perhaps without the dramatic ups and downs of transplantation. Amniocentesis was the first test to be developed and this required a number of scientific and methodological developments: the understanding of human chromosomes, identification of the genetic defects associated with Down's syndrome, the ability to culture amniotic cells for chromosome analysis and the equipment and skill development to obtain amniotic fluid transabdominally with safety. In the 1960s a number of European countries experimented simultaneously with amniocentesis, including some countries where the abortion laws at that time meant that the purpose could only be investigative. The drawbacks to mid-trimester diagnosis led to a search for a test which could be done earlier in pregnancy. First-trimester sampling of placental tissue was tried in 1968, and unsuccessfully a number of times throughout the 1970s. It took until the early 1980s until chorionic villus sampling developed fully. This required the combination of the development of a fine cannula with the use of ultrasound so that the villi could be located and the procedure performed safely.

Ultrasonography is both a screening and a diagnostic technique and a support to the other technologies. It emerged from a different setting, naval warfare. The potential for clinical application was recognised in the 1920s and 30s. Obstetric ultrasonography was pioneered by Donald in Glasgow and the first papers were published in the late 1950s. This was only the beginning: the image produced had to improve significantly for clinical use and it was only in the 1980s that real time ultrasonography was widely introduced.

Finally, MS-AFP assay again had different origins. AFP was recognised as a fetal product in 1956. In 1972, reports came out of Japan that MS-AFP concentration was higher than normal in an anencephalic pregnancy and, from the UK, that amniotic fluid AFP was higher in the presence of fetal open spina bifida or anencephaly. Thereafter screening began, with a large-scale collaborative study in the UK in 1975, and in Denmark, FRG, The Netherlands and Sweden at the same time.

Though both are used in renal stone treatment the two techniques of PCN and lithotripsy came about through rather different routes. PCN is based on endoscopy and over a period of time the users (surgeons) were working closely with manufacturers to design the requisite ever smaller instruments. Lithotripsy was one of the medical innovations which developed from research in another sector, in this case defence (like ultrasound). The German firm Dornier had a research grant from the Ministry of Defence to study the interaction between shock waves and tissues in animals. The relevance to medical care, specifically kidney stone treatment, was noted but this required a means to reach stones without destroying the intermediate tissue. Once the idea of focusing the shock waves was developed, a prototype was possible.

Because of the links during the developmental phase, the prototype went into the Munich University Hospital in 1982, around the same time that PCN was reaching maturity as a procedure.

The technologies in the study illustrate then both technology-push and the need-pull developments. Transplantation and PCN were very much driven by the perceived need of doctors and scientists for their development. Lithotripsy came much more 'out of the blue' from work in another area, just as CT scanning came out of the entertainment industry.

Early adoption

It is already clear from innovation development that the same countries appear repeatedly. The country of origin of the innovation may vary, but the group of countries who are either the innovators or the early adopters is fairly constant. These are mainly the northern European and Scandinavian countries – with, of course, the USA also in the forefront.

Tables 1 and 2 show the start of heart and liver transplantation respectively. Most surprising is that Denmark did not start heart or liver transplantation until 1990. Why this delay occurred is discussed in a later section. Table 3 shows the dates of introduction of lithotripsy. Data on the spread of PCN across countries is not available although Sweden, Germany and the UK were among the first countries to report use.

Table 1
The start of heart transplantation in EC countries

Category	Country	Year of start
Innovators (1967–1970)	(South Africa)	1967
	USA	1968
	France	1968
	UK	1969) stopped
	FRG	1969) 1970
Early adopters (1973–1984)	UK	1973
	FRG	1981
	Belgium	1982
	Sweden	1984
	Netherlands	1984
	Spain	1984
Late adopters (1985–1990)	Italy	1985
	Ireland	1985
	Portugal	1986
	Denmark	1990
	Greece	1990
Not yet started	Luxembourg	

Table 2
The start of liver transplantation in EC countries

Category	Country	Year of start
Innovators	(USA)	1963
(1963–1970)	FRG	1968
	France	1968
	UK	1968
	Belgium	1969
Early adopters	Netherlands	1977
(1975–1983)	Italy	1981
Late adopters	Spain	1984
(1983–1990)	Sweden	1984
	Ireland	1985
	Portugal	1987
	Denmark	1990
	Greece	1990
Not yet started	Luxembourg	

Table 3
Uptake of lithotripters in EC countries

Category	Country	Year of start
Innovator	FRG	1982
Early adopters	UK	1983
	France	1984
	Italy	1984
	Spain	1984
Late adopters	Netherlands	1985
	Sweden	1985
	Belgium	1986
	Greece	1986
	Ireland	1987
	Denmark	1987
	Portugal	1987

Finally, Table 4 shows the introduction of the three prenatal screening technologies. Here it is interesting to note that amniocentesis was introduced fairly slowly over about seven years. The reasons seem to be that the procedure required the establishment of an infrastructure of clinical genetics services which most EC countries did not have at that time. In contrast, CVS was introduced rapidly primarily because that infrastructure was now in place. A change in abortion laws also seems to have been necessary for amniocentesis to be taken up. That factor was probably even more influential in the spread of diffusion within a country than in the first attempts with the technique by innovators. Much less information on MS-AFP testing was given by the country rapporteurs, perhaps because many countries do not have a programme.

Table 4
Introduction of prenatal screening technologies in the EC and Sweden

Amniocentesis		CVS		MS-AFP	
UK	1969	UK	1982	UK	
Denmark		France		Denmark	
FRG	1970			FRG	1974
Netherlands		Belgium		Netherlands	
Spain		Greece	1983	Sweden	
Belgium	1971	Spain		Belgium	1975
Portugal	1972	Denmark		Greece – date unknown, no screening, but some amniotic AFP measurement	
France	1973				
Italy	1975	FRG			
Greece	1976	Netherlands	1984		
Sweden	1970–1	Portugal		Portugal	no
		Spain		Spain	infor-
				Italy	mation
Ireland – no organised screening programme				France – no national programme but some undertaken	
Luxembourg – none undertaken within country, counselling and screening tests referred to other countries.					

Innovation diffusion

In the stories of the development of the three technologies many of the same countries reappear as being at the forefront of scientific and medical development. It does not necessarily follow that the innovations diffuse quickly in these same countries. In this respect the UK stands out as unusual in often being an early adopter but then lagging behind in the later diffusion.

Table 5 shows the number of lithotripters installed each year. The equipment was developed in the FRG so it is not surprising that diffusion took place there first and that that country was still in the lead per head of population in 1990. Many countries have more machines than national plans suggested was necessary. The drawbacks for urology departments in not having their own machine were such that many of them went ahead anyway, outside national planning agreements, eg in Sweden. Contrast this with the UK: it purchased a lithotripter very early on but diffusion has been very slow, with UK and Portugal at the bottom of the table per head of population by 1990. Even having been the country of origin of the innovation does not mean that the UK keeps up in the diffusion process. This is well demonstrated by the figure for CT scanners: the British firm EMI developed the first CT scanner in the

Table 5
New installations of ESWL by year

Country	1982	83	84	85	86	87	88	89	Total
FRG	1	3	8	7	5	12	16	20	72
UK		1		1		6	3	4	15
Italy			1	6	3	11	27	21	69(74?)
Spain			1	7	1	11	14	16	50
France			1	2	7	16	3	7	36
Netherlands				1		2	5	3	11
Sweden				1			3	2	6
Belgium					1	3	7	1	12
Greece					1	2	3	4	10
Denmark						1	1	1	3
Ireland						2			2
Portugal						2	1	1	4
Europe	1	4	11	25	18	68	83	80	290

The numbers shown do not correspond to the present number in operation, a few of the first-generation machines having already been taken out of service. Danish-made NITECH machines are not included: two were being installed by the end of 1989. A further five Siemens machines are believed (according to information from the manufacturer) to be in operation in Italy, but since their location could not be ascertained they are not included. A few of these lithotripters are used exclusively or primarily for gallstone treatment (although gallstone lithotripters are capable of disintegrating kidney stones provided these are detected by ultrasound), so that the number at the disposal of kidney patients is somewhat lower than that shown.

UK in 1973, but by 1986 the UK was well down the European table.[1] Similarly, the UK was an early developer of kidney dialysis and transplantation but there have been repeated concerns over the years that it is not keeping up with its European neighbours.

In part this may be explained by the funding constraints on the NHS in Britain. Compared to the other northern European and Scandinavian countries with similar scientific and medical development, it is both a less wealthy country and spends less of its GNP on health (around 6 per cent over the last few years). This cannot, however, be the only reason. After all, Table 5 shows how quickly Greece, and, particularly, Italy, were able to catch up – both countries with relatively poor health services compared to northern Europe. There is clearly something about the way the capped budgetary system operates in the UK which is unusual. It probably has to do with a sense of competing needs at local level within a local budget, and also the difficulties in acquiring large capital sums for equipment purchase. Certainly those technologies requiring significant capital investment such as CT, MRI scanners and lithotripters have been slow in diffusing in the UK.

Returning to the lithotripter, Table 5 illustrates clearly the problems of a monopoly supplier. Diffusion was slowed by Dornier's capability to deliver, its capacity being about 15 per year in 1986. The diffusion was also slowed by governments' and funding bodies' adoption of a wait-and-see policy, especially as cheaper machines were known to be in development. The innovation took off when in 1986 a number of these machines from other companies became available and when some countries, e.g. Belgium, removed some of the controls on purchase (towards the end of that year).

Another feature of innovation diffusion can be seen in Table 5: the north–south Europe divide. The northern European countries developed and took up the innovation early on. Southern European countries, though, while

Table 6
Date of introduction of amniocentesis into EC countries and Sweden

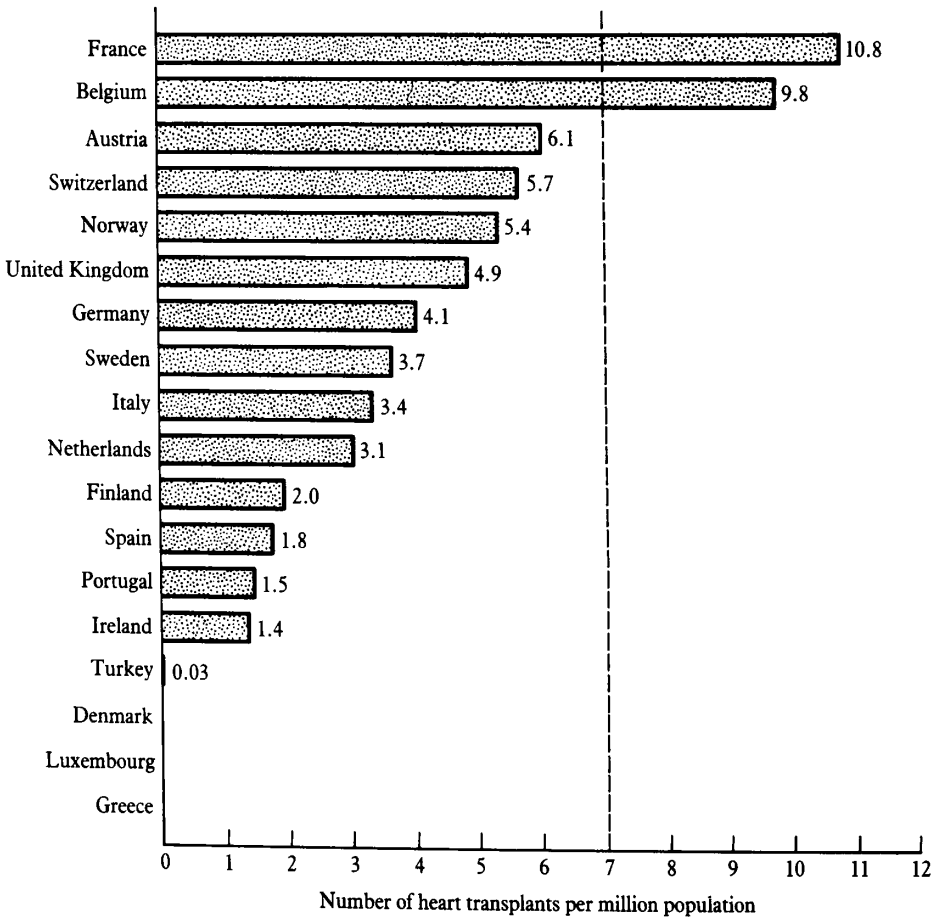
Country	Year
UK	1969
Denmark	1970
FRG	1970
Netherlands	1970
Spain	1970
Belgium	1972
Portugal	1972
France	1973
Italy	1975
Greece	1976
Sweden	1970–71

Source: Country reports

starting late, may leapfrog a stage and catch up fast. It is in the diffusion of prenatal screening technologies that this feature appears perhaps most clearly (Table 6). Reid, in her overview of these technologies, puts forward a number of possible explanations. These include having the scientific intrastructure and the research funds for clinicians and scientists to travel to international meetings, but also to start new tests on their return. Sources of research funds include those in industry, again more likely in the more industrialised countries. Such private backing was crucial in a number of countries in getting the innovation started.

These economic features are the general background to the diffusion of many medical technologies, but particular influences on prenatal screening were cultural and religious differences. Reid points out that attitudes to screening are closely related to those on abortion, and the southern European

Figure 2
Heart transplantation rate in European countries in 1988 (ranking according to number of transplants per million population)

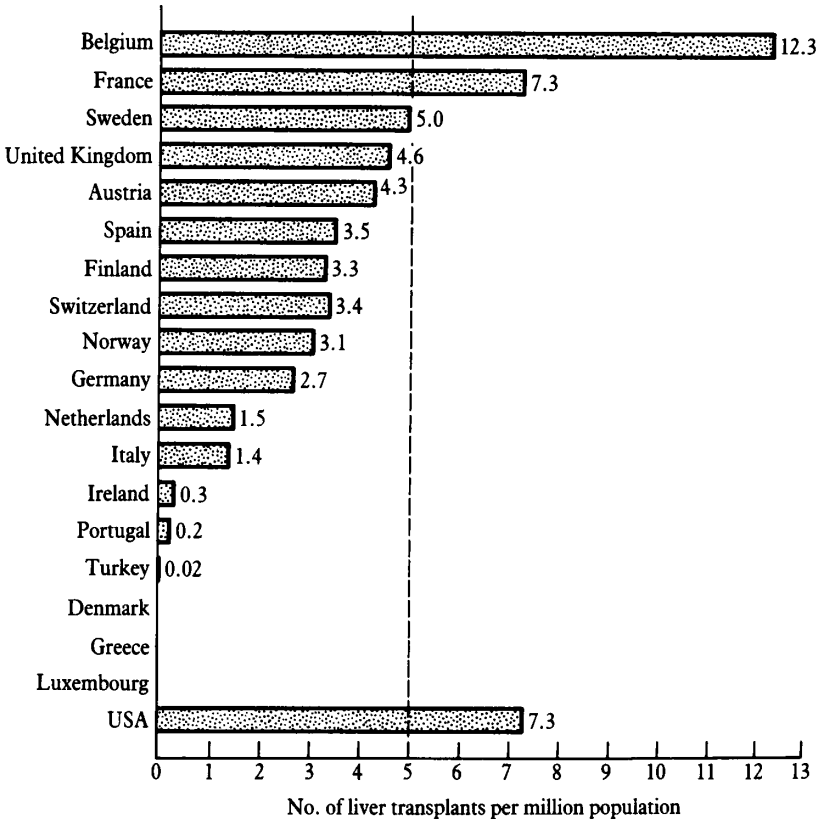


countries have been more influenced by the Catholic Church. As always, there are exceptions to the rule. While Belgium had until very recently very restrictive abortion laws this did not stop prenatal screening (nor, it seems, abortion of defective fetuses) from taking place.

The diffusion of heart and liver transplantation confirms a number of points already mentioned. The countries with a long-standing tradition of scientific interest in transplantation and immunology (France, UK and W.Germany) were pioneers. However, they are not necessarily the countries which have developed the largest clinical programmes. Belgium, for example, has overtaken both the UK and FRG. Figures 2 and 3 illustrate the position for heart and liver transplantation in 1988. Some of the southern European countries such as Spain, Portugal and Italy, have made very rapid progress although they were relatively late in starting these procedures. These same countries were also later in organising national or regional organ procurement arrangements.

Figure 3

Liver transplantation rate in European countries in 1988 (ranking according to number of transplants per million population)



Sources: US Department of Health 1990; European Liver Transplant Registry 1989.

A feature that is masked in these tables, however, is the number of centres undertaking transplantation, which is quite variable even among countries undertaking comparatively similar numbers of procedures. For example, in the UK, Belgium and Spain a single centre performs the majority of liver transplantations. This contrasts with France, where a large number of centres operate. The Scandinavian countries, the Netherlands and the UK have policies which have encouraged 'national referral centres' rather than the proliferation of centres.

Appropriateness in use

Given the uneven but fairly wide diffusion of most technologies in this study, are the right people receiving the technology to get the most benefit even within the limits of diffusion?

According to early estimates of need based on the number of open procedures, Europe is over-endowed with lithotripters. There are few data on which to draw, but what exists suggests that the clinical indications for stone treatment have been widened, so that asymptomatic stones are being treated as a preventive measure. The appropriateness of such treatment has not been established. Also it seems that some people who might be considered as good candidates for lithotripsy are receiving other treatments, especially PCN. In part this may depend on poor access to lithotripters. Geographical access is a factor, but more important probably is the willingness to refer. Some urologists who do not have lithotripters themselves may perform PCN rather than refer their patients to a lithotripsy centre. Overall then, despite a high level of provision there is the impression of a less than rational use of the technology – although evaluation data are still lacking to define appropriateness more rigorously.

That geographical and informational access is an issue emerges strongly from the prenatal screening study. While all but two EC countries undertake amniocentesis this has not reached saturation level in most countries, and there is considerable within-country variation. Women living near capital cities (especially in France, Greece and Spain) and those with higher levels of general education appear from some surveys to have greater access to the test. Reports from the UK and Italy also indicate little correlation between a region's population and the number of cytogenetics laboratories. However, again it seems to be the attitude of referring doctors that is the most important factor, although that may be influenced by laboratory capacity, distance from centres, and so on.

The funding mechanisms of the countries might be thought to be a factor in the availability of the amniocentesis. However, despite disparate systems of funding all countries report uneven distribution of the test, and it may not necessarily be those at greatest risk who are obtaining amniocentesis.

MS-AFP screening is even more variable. Different countries have taken different positions. None has routine MS-AFP testing in all regions, although the UK is probably closest to it. The country distribution only partially correlates with incidence of neural tube defects.

Transplantation is the technology in this study where the clinical indications

have been examined most thoroughly. The indications are continuously expanding, however, and no country is yet at saturation point for kidney, heart or liver transplantation. Diffusion is limited not only by finance but primarily by the availability of organs for transplantation.

3 THE CHARACTERISTICS OF THE TECHNOLOGIES THEMSELVES

The technologies were included in this study because of rather different characteristics.

Prenatal screening

The tests are relatively cheap individually, though they cover a significant population. Little capital is required to start doing the tests and, apart from ultrasonography, there is little emphasis on equipment. Because of the ethical issues involved it was considered that consumers might have a greater influence here than with the other technologies.

Stone treatment, particularly lithotripsy

For lithotripsy a large, expensive item of equipment is involved, so it was expected that government regulations might play a significant part, as well as industry itself.

Organ procurement and transplantation, focusing especially on heart and liver transplantation

Because the resources required to set up a programme are significant it was again expected that governments and funding agencies would be influential. The procurement aspect also raises complex ethical issues.

By taking three rather different technologies we hoped to identify the commonalities and differences between them.

Some of the expected issues did turn out to have influenced diffusion. Small, cheap items did mean that there was freedom to innovate quickly without waiting for major funding. The initial diffusion of prenatal screening tests was then much more professionally determined than for the lithotripter, where national policy-makers become involved. It was often the availability of research funds or the ability to 'add on' an extra test which meant that prenatal screening tests were able to diffuse. However, sometimes governments provided the funding to get programmes going, for example, in Greece and Denmark. Liver and heart transplantations fall somewhere between the other technologies. They require considerable organisaton and funding and were such dramatic developments that governments became involved from early on. It was not the setting up of national advisory groups etc. by governments which made diffusion a fairly slow process, but the fact that only a small number of sites were capable of undertaking these procedures.

Thus, another characteristic emerges: whether the innovation requires a complex infrastructure or not and, if so, whether this infrastructure is needed generally or only at specialist centres. Lithotripsy could in theory be used in any urology department, so the infrastructure was already in place and fairly widespread. Transplantation required highly specialist skills, but many EC

countries already had a few centres and that level of expertise. Prenatal genetic screening did in the early days require the establishment of genetic centres. Initially, then, the spread was fairly slow but once that infrastructure was in place it was relatively easy to add in the new screening and diagnostic tests of MS-AFP and CVS.

The other key characteristic which emerged in the study had to do with perceived benefits, and the extent to which the technological imperative dominates: that is, 'if it can be done it should be done'. One might expect this imperative to be very strong with life-saving technologies. However, of the technologies in this study, transplantation falls most neatly into that category, yet its diffusion is not obviously much speedier. The constraint was at least partly about the risk-benefit ratio and about cost. Early on, heart and liver transplantation were not obviously 'life-saving' because the survival rates were poor. There were long periods of development for transplantation of all the organs in this study. The technological imperative only really begins to show with kidney transplantation, which is in a later stage of development. European countries seem to have decided that either transplantation or dialysis should be offered because they are life-saving, and that transplantation is preferred because it is more cost-effective, with a better quality of life for patients. There are, of course, still rationing issues and these have evolved over time.

The other two technologies are less clearly 'life-saving': prenatal diagnosis is about identifying handicapped fetuses and usually offering the option of abortion; lithotripsy was simply an alternative form of stone treatment. Both technologies did have imperatives of their own. In his overview, Kirchberger describes the use of economic or patient-benefit arguments which the innovators made to try to get lithotripters purchased. Compared to open operation there are obvious benefits, since the procedure is much less risky and the length of stay shorter. But as Kirchberger notes, many of the centres arguing for a lithotripter had already moved on from open operation to percutaneous treatment, which compares much more favourably with lithotripsy. The doctors arguing for lithotripsy may well have felt it was of benefit to patients compared to PCN but the arguments seem to have focused on the comparison with open surgery. Surprisingly too, governments seem to have accepted the arguments, and the debates were not about comparative cost-effectiveness, or there would have been more calls for clinical trials, but about how many lithotripters were needed, where they should go, and manufactured by whom.

The prenatal tests illustrate most clearly the concern about risks versus benefits. Although the need for diagnosis of defective fetuses comes out clearly in the reports as being an imperative, the difficulty arises with the concomitant risks – risks of miscarriage of normal fetuses with amniocentesis and CVS, risks of false negatives with MS-AFP, etc. Thus the risks of amniocentesis had to be reduced before it was accepted nationally in several countries, the risks of CVS compared to amniocentesis are being clarified, and the risks of false positives and false negatives of MS-AFP have to be weighed up, especially in places where there is a low incidence of neural tube defects. Only ultrasound appears as a risk-free technology and even with it,

Table 7
Characteristics of the three technologies as innovations

	Prenatal screening	Heart and liver transplantation	Lithotripsy
RELATIVE ADVANTAGE	Risks high in early days. Benefits: allows abortion of affected fetuses or preparation for handicapped child	Lifesaving but in early days survival poor	Alternative non-invasive treatment
COMPLEXITY	Quite complex to organise on national basis – involves different groups of doctors (GPs, obstetricians, geneticists)	Complex to organise as service – requires link to organ procurement agencies	Relatively straight-forward – remained in the domain of the urologists
COMPATIBILITY (with roles, beliefs, etc.)	Variable – very incompatible where abortion laws had not been liberalised	Compatible once brain-death issue resolved	Very good, did not pose major threats to beliefs
OBSERVABILITY	Not very visible	High media profile, therefore very 'observable'	Partial, publicly this depended on clinicians getting media attention for lithotripters. Within medical profession, high. Urologists travelled to see centres.
TRIALABILITY	Techniques could be tried out in particular centres	Yes, surgeons were able to experiment	Low. Had to purchase machine, could not try out on a small scale.

there have been some doubts about its long-term effects. Consequently, of these tests, ultrasound is the one which has diffused most completely through the EC health care systems.

These are some of the characteristics which emerge from the reports about the three technologies. There has been much work done elsewhere on the diffusion of innovations, and Rogers[2] has produced a summary of what he concludes are the key factors affecting diffusion: relative advantage (of the innovation over its comparators), complexity, compatibility, observability and trialability. It is interesting to analyse the three technologies according to these characteristics. As would be expected, since all of them have diffused to a considerable extent through EC countries, they all come out in a fairly positive light. Table 7 shows some of the contrasting features.

Relative advantage has been discussed. Complexity appears as an inhibiting feature for prenatal screening and transplantation because of the need to develop a service infrastructure. There were also difficulties in compatibility with belief systems in some countries for both these technologies. Observability is interesting and highlights the difficulty clinicians (or others) may have in countries where there is less opportunity to travel to international meetings or to the centres of innovation. Only for transplantation has media attention produced general awareness of the technology. Finally, trialability of two of the three technologies was high. It had to be for both prenatal screening and transplantation – in neither case was a fully developed technology available in the early days of diffusion.

4 THE COUNTRY CONTEXT

Critics of national health services might say that they lead to severe rationing, waiting lists, and a resistance to entrepreneurialism and change. Critics of pluralist fee-for-service systems might say they lead to the rapid and wasteful diffusion of totally unproven technologies. Variations on these types of health systems are the context in which the technologies in this study diffused, so how far are the critics' worst fears shown to be justified?

First, the health systems do not fall into quite such neat categories. Those with national health systems range from Scandinavian countries where there is much local democratic control, with local taxation a key source of funding but a great deal of adherence to national planning agreements, via the UK where in theory there is a monolithic health system but in fact quite significant local control and local variation, and Italy with a relatively new national service but with a large private sector caring for publicly funded patients, to Spain, Portugal and Greece attempting to pull together fragmented health care into a national system.

Equally those systems based on health insurance have great variability. West Germany is at one end of the spectrum, with its emphasis on independent medical practitioners outside hospitals and little national health care planning. France is somewhere in between, with insurance systems but much hospital care taking place in the public sector, and there is The Netherlands, with its national health insurance systems and considerable governmental control over the whole system.

Chapter 2 showed, however, that the diffusion of the three technologies does not fit a simple pattern. There is no direct correlation between the general type of health systems and the speed of diffusion. It seems that the incentives operating are more complex and it is in the detail of the systems' operations where these incentives can be seen to be influencing events. Some of the overall country characteristics which emerge as influencing diffusion may be as much to do with cultural characteristics and attitudes towards health care and to the medical profession as with features of the health system.

One influence which cannot be ignored is the country's wealth. As already demonstrated, there is a north–south divide in the uptake of new technologies, not merely reflecting the finance available in the health system, but also the availability of funds from industry, charities, etc.

A second characteristic concerns the different assumptions over the rationing of care, and the criteria which determine who should receive some medical technologies. For example, in the early days of a new technology when it is severely rationed in any country, it is common to include age limits in the eligibility criteria. In general these restrictions become less stringent as the technology diffuses. However, the UK stands out as a country which has operated such criteria more noticeably than others. The criteria have sometimes been quite explicit, sometimes more implicit in the way doctors have refused patients. A number of researchers have been interested in the way the UK has managed to ration the life-saving procedures of kidney dialysis and transplantations.[3,4]

There are also less tangible issues about the willingness of the health

system, and especially doctors, to conform to general policies and controls. All European countries are concerned about the rising costs of health care and are taking a variety of measures to contain costs, including controls over expensive medical technology. The impact of these regulations on the introduction of the three technologies is described below. However, a more general point emerges, which is that in some countries it seems to be more accepted that controls on medical technology are inevitable, even if not liked, and that evaluation of their benefits is an important prerequisite. The two countries which stand out most clearly in this regard are The Netherlands and Sweden. These are both countries where there is considerable state domination of services. For example, there is little private health care or private education. Both countries have gone further than others in establishing mechanisms for the assessment of new technologies. In addition there seems to be an agreement that decisions about widespread diffusion should await the results of trials. This rationality should not be overstated, since in both cases there are instances of events where the general conformity with policy was broken. Denmark also seems to fit with these countries in terms of research mindedness; it also seems to be possible there to question practices without this being seen as extremely threatening.

Aside from the intricacies of health system functioning there are other social and cultural characteristics which influenced the three technologies, and these concern attitudes towards life and death. The two major examples are (a) the debates about abortion and their effects on the diffusion of prenatal genetic screening, and (b) the debates about the criteria for death and its implications for the availability of organs for transplantation.

Amniocentesis was developing at a time when a number of countries were liberalising their abortion laws. Some people have suggested that these changes were a prerequisite for the acceptance of amniocentesis. Certainly, countries with restrictive laws against abortion in the main did not develop genetic screening services. However, it may have been that discussions about screening were also influential in changing the laws themselves. Cause and effect is not clear-cut.

It was mainly Catholic countries which were strongly opposed to abortion, and only recently have they changed their laws. Ireland still has not done so. However, in recent years differences amongst Catholic countries have emerged. Belgium is the most interesting, with a developed system of prenatal screening even though abortion was, until 1990, illegal.

Spain, Portugal and Italy fall somewhere between the extremes of Belgium and Ireland, with development of some services but with referrals highly dependent on the view of individual doctors about abortion of affected fetuses. For example, in Italy when abortion was first legalised 72 per cent of doctors were recorded as conscientious objectors to it.

Although abortion is the main issue, another cultural difference which emerges in prenatal screening, and in organ transplantation, is the involvement of society in debates about medical technology. For example, in some northern European countries newspaper and TV have been very active in promoting discussions about ethical issues around life and death. Others, such as Spain and Portugal, had severe restrictions on the press until recently,

reducing the role of the media in providing information about developments in medical technology and in reflecting and influencing societal opinion.

The media, particularly TV, have been heavily involved in the debates about brain death in at least two countries, the UK and Denmark. Only in 1990 did liver and heart transplantation begin in Denmark because the criteria for brain-stem death were not accepted and these transplantations require organs from heart-beating donors. Danes did, however, receive transplants in other countries. As expected, this led to some controversy outside Denmark since they were not contributing to the pool of donor organs but were receiving the benefits.

5 INFLUENCES ON THE DIFFUSION PROCESS

GOVERNMENT AND NATIONAL FUNDING AGENCIES

Governments would rather not have to make decisions about new medical technology. The impression in this study is that if the professionals could agree amongst themselves, governments did not want to be involved. This in part explains why diffusion may commence quite briskly, even with quite expensive technologies, and then suddenly governments or funding bodies such as Sickness Funds wake up to the implications and have to play a part. The other reason for the delay might be that governments do not have early warning systems about new technology – The Netherlands being an exception with its Steering Committee on Future Health Scenarios. Nevertheless ministries of health do contain informed people who know what technology is being developed, so the lack of early warning does not stand up as a good reason for the delay in response.

The underlying factors which persuade governments to become involved are: where there are identifiable costs, and governments are concerned that the innovation may diffuse rapidly and expensively; where major issues of life and death are involved (even this sometimes requires considerable media exposure before governments feel obliged to play a part); and where issues of equity emerge (e.g. geographical access is unbalanced, the private sector is already offering the service but it is not available in the public sector, etc.).

Once alerted, governments and funding bodies then take a number of steps. They will certainly take advice, and at present this seems to be mainly from the professionals concerned and their representatives. They may set up advisory groups or refer the issue for opinion to bodies established for that purpose, e.g. the Health Council in The Netherlands. Such advisory groups have been established for all three technologies in this study in one country or another. For liver and heart transplantation the majority of countries have had some sort of review. Governments may then try to ensure that evaluation takes place. This is quite variable from country to country and by technology, and is taken up in a separate section.

The question then is how do governments (or funding bodies) use the various regulatory instruments at their disposal to control or at least influence events? As reported in the earlier EC study on regulatory mechanisms[1], EC countries fall broadly into two categories: those which operate some form of global budgeting, often devolved to regional or lower levels, but with national or regional planning agreements; and those much closer to fee-for-service financing, where medical technology is usually controlled through central regulations requiring approval for purchase of major items of equipment, or sometimes for procedures, and through reimbursement regulations. The overall conclusion in the previous study was that if the general damping down of diffusion is the aim, the global budgeting approach is more successful. However, it is fairly indiscriminate, not necessarily sorting out technologies with good cost-effectiveness from poorer ones.

How then have these regulatory mechanisms been applied with the three technologies in this study, and how effective have they been?

Transplantation

Transplantation requires specialist skills and facilities. It does not, though, require major capital investment. The regulatory mechanisms to be used by governments and financing bodies over transplantation fall broadly into three groups:

National planning agreements
These are mainly in countries with global budgetary systems. In particular, Denmark and Sweden have planned their transplantation centres on a national basis. The UK is somewhat different. Although the initial transplantation centres received some earmarked funding, there are no controls, other than financial constraints, on the start-up of new centres.

Specific medical technology regulations
The Netherlands, France and Belgium all have specific regulations over medical technology. In The Netherlands this covers services as well as equipment, and transplantation has been well controlled. However, transplantation is outside the scope of the list in Belgium and France and there are no governmental controls. In France, however, France-Transplant approves centres for transplantation.

Transplantation laws
A number of later adopting countries (Spain, Portugal, Italy and Greece) have laws specifically relating to transplantation and these require centres to be approved before transplantation is allowed.

Finally, the FRG stands out as quite unusual in that there is no formal planning applied to transplant technology, although the National Dialysis Foundation (KfH), a private charitable organisation, influences diffusion through financing arrangements with the Sickness Funds.

While a variety of control mechanisms have been applied, only in a few countries is transplantation highly regulated. The one common issue is that regulations have ensured that most transplantation takes place in public hospitals rather than in the private sector.

Lithotripsy

Again, the types of regulatory approaches can be divided into a number of broad headings:

National systems with global budgets
In several of these countries (e.g. Denmark and Sweden) there were attempts at national planning of lithotripsy. In Denmark it was agreed to hold back diffusion until County Councils could obtain a nationally produced machine, but production was so long delayed that eventually the agreement was broken. In Sweden agreement lasted through a long phase of assessment of the first machine. However, even though it was then agreed the country needed only three machines, twice as many County Councils proceeded to purchase them.

In the UK, which falls into this category of system, there were no controls over lithotripsy other than financial constraints.

Regulated equipment lists
In these countries lithotripters did appear on the lists and so their diffusion could be controlled. How these controls were applied varied: in Belgium regulations were interpreted very generously; in France the regulations were used to control (indeed, virtually exclude) entry of foreign machines into the home market; in The Netherlands, where control might have been expected, there is none except it is agreed that budgets cannot be increased to cover costs of lithotripsy. This has led to relatively constrained diffusion, with groups of hospitals purchasing a single lithotripter.

No controls, or controls only in the public sector
In the FRG and in southern European countries there was little attempt to control the diffusion of lithotripters. In the FRG, individual states may have certificate-of-need legislation, but sickness funds may still pay even though equipment has not been agreed, so there is no control over diffusion. In Greece and Italy, there is control over purchase in the public sector through central financing. However, the private sector is unconstrained, even though it is often the public purse paying for treatments.

Overall there appears to be less successful control over the diffusion of lithotripsy than transplantation, despite the fact that it is a large item of equipment which falls unequivocally under various regulations. It may be that governments were easily persuaded of the benefits of lithotripsy. Other factors, though, include the lack of regulation over private sector purchase. Finally, as a relatively new technology it has been subject to the recent movement of some countries such as The Netherlands towards global budgetary controls and away from specific regulation of particular items.

Prenatal screening

The earliest test under this heading to be introduced was amniocentesis. In its early stages no governmental intervention was necessary: the test is small scale and not exorbitantly expensive, so it was possible to begin by using research monies. To establish a national genetic screening service required formal representations to government because at that time, about 1970, the necessary infrastructure of genetic centres was not available. In several countries (Sweden, FRG, Denmark and France) groups of doctors drew up blueprints of what was required and this is what broadly came about. Reid notes, however, that in many countries amniocentesis has never been given a formal stamp of approval, perhaps because of the often unspoken link with abortion, but has been left to develop without a strategy.

Thus government controls were less concerned with the early diffusion of the technology than with its general availability. A number of countries, notably, Greece and Portugal reported that resources had not increased to meet the rise in demand. Prenatal screening is rather different from the other technologies in the lack of use of regulations and planning mechanisms.

In conclusion, there are contrasts with government involvement in the regulation of these technologies, and their outcome. In the FRG there have been few if any central government controls, and diffusion has been relatively uncontrolled. In contrast, in the UK diffusion has been contained without a great deal of central government involvement, but through local budgetary constraints.

In countries where there have been specific medical technology regulations they have not been applied uniformly, either across those countries (France, Belgium, The Netherlands) or across the technologies. Denmark, and especially Sweden, stand out as the countries which have gone furthest in national planning for these expensive technologies, yet even there agreements have been breached.

PROFESSIONS

Policy makers and managers are well aware that it is the health professionals – usually doctors – in a particular field who develop or are the first to know about a new technology. It is these professional leaders who lobby them intensively for the resources or the permissions required to go ahead. It was therefore not surprising that the role of doctors in introducing technology into a country comes out strongly in this study. However, the approaches used by doctors for each technology and each country differed.

Lithotripsy

Key urologists began to visit Munich to see the lithotripter development as early as 1978/9. The first visitors brought the message back to their own country and began to lobby the relevant funding and decision-making bodies.

However, the next stage was not so straightforward. Only a few lithotripters would be needed in each country, and in any case Dornier had a limited production capacity. Only a few hospitals would therefore be likely to get the machine. In Denmark this resulted in agreement amongst key urologists that they would all wait until Denmark was able to produce its own machine. This seemed to be on the basis that if purchase were to go ahead immediately only one would get a machine, but if they waited several of them were likely to be satisfied. The agreement was weak, though, and in due course broke down.

In France the agreement was that since there was only likely to be one machine in the Assistance Publique hospitals of Paris, all ten urology departments should have access to it. Also, since its presence would put any one hospital at a considerable advantage, it was suggested that the site selected should be 'neutral', that is, not one of the urology departments. Further discussions showed this to be a rather impractical approach and in the end the Assistance Publique had to step in to decide on the location, which was in one of the hospitals but in a separate department from the urological service! Belgium followed a similar path, a military hospital being selected as the neutral environment. Again, this was highly unsatisfactory and discussions on purchase were delayed until eleven machines could be ordered in quick succession at the end of 1986.

This essential point about monopoly of use and the associated prestige was demonstrated in other countries too. A technology which is costly, limited by production or by legislative agreement is one which decision makers will undoubtedly need to take professional advice about. Equally, these characteristics make it unlikely that there will be consensus from the profession, especially about appropriate location.

Prenatal screening

Reid states in her review of prenatal screening procedures that the key people in their diffusion are members of the medical profession. Because the specialty of clinical genetics was not very advanced two decades ago they tended to be paediatricians or obstetricians. These individuals did not simply have to argue for a particular test but for the setting up of genetics services as a whole.

The early innovators often worked hard with the media and the public as well as with national policy makers. For example, the West German innovators worked to change the negative image of genetics following the Nazi era. They maintained a high press profile and encouraged meetings for lay audiences as well as scientific meetings. In Sweden, similarly, a small group of specialists in clinical genetics also put a great deal of work into 'selling' genetics.

Despite the professional enthusiasm in some countries, both for getting these services going and in ensuring that good assessments of safety and efficacy were undertaken, these same doctors could also be much more negative gatekeepers. Although in principle most people agree that first-trimester diagnosis of Down's syndrome would be preferable, when CVS was introduced neither its risks for the mother and for fetal loss compared to amniocentesis nor the risks of transabdominal versus transcervical CVS were known. An international meeting was held which agreed that CVS should not follow the pattern of unevaluated introduction which had been the case with amniocentesis, but that an attempt at central coordination should be made and that a a randomised clinical trial should be set up. Although the trial was set up and a number of northern European countries and Italy took part, some of the Italian centres dropped out of the trial and in general there was wavering commitment to the need for a trial. The German leaders argued that a trial was not needed because, as in the case of the lithotripter, CVS was self-evidently better.

The role the key figures play may depend on their personal interests. For example, the first centres taking up CVS obtained much 'kudos' but, of course, the next ones would not have the same status. In some places, then, leaders argued for and began attempting early amniocentesis instead of CVS. This competition for prestige is, of course, a great spur to scientific advancement, but it does not make for the most rational approach to the introduction of medical technology.

Another aspect to be considered is what happens when key figures are unenthusiastic about the technology. This seems to be what happened in France for CVS. The risks were thought to be high and, without a leader to

push forward the arguments, CVS has been left at a fairly low level.

These examples all illustrate doctors operating politically through whatever channels are available: press, scientific journals and meetings; national working parties and, as much as anything, informally behind the scenes. Their other role is, of course, with the individual patient. They may give information about particular tests or they may withhold it. Even if the patient is informed, doctors may be very influential in making or blocking access to services. There is strong evidence in the country reports (Italy, Spain and Portugal) that doctors are very influential in whether women get prenatal screening or not. In several countries, particularly Catholic ones, there are conscience clauses to permit doctors who do not wish to be associated with abortion to decline to do so.

Organ transplantation

Again, the coordinator, Bos, states that without exception the leading role in kidney transplantation was played by the medical profession. Only 10–15 years after the first transplant did governments and financing bodies become involved – mainly because kidney transplantation provided a better and more cost-effective solution than dialysis. In some cases governments, for example in Scandinavia, became involved in arrangements for organ procurement, but in others it was again doctors who promoted national networks for exchange of organs.

Similarly with heart and liver transplantation, decisions about where to start transplantation were taken by individual clinicians or transplant teams, often without any involvement of local health administrations or national bodies. Because of the publicity surrounding transplantation, many of the transplant surgeons became public figures. As governments became involved, which they did rather earlier than in the case of kidney transplants, many of these same clinicians served on national advisory bodies.

HEALTH PROVIDERS

Although professionals have been shown to have taken a leading role in the introduction and diffusion of technology, they may or may not have been supported by administrators/managers in the health settings where they operate.

For example, in countries where the private sector plays a large part in the provision of health care there is usually a strong incentive for them to take up a new technology. It is not simply a matter of prestige; a hospital may also stand to lose patients if it does not have the technologies which are available elsewhere. In several countries, too, while the public sector is subject to budgetary constraints or to regulatory controls, the private sector may be free from restrictions. For example, lithotripters in Greece and Italy are mainly in the private sector which is unconstrained in its purchase of equipment. Even if public sector patients have access to treatment it still leaves the government with difficult issues about distribution of the technology.

An interesting issue arose in Barcelona where there were adequate numbers of lithotripters in the private sector but because of the cost involved in paying for patients to be treated, the regional government decided to purchase additional lithotripters for public hospitals.

The hospital administration may not always operate in line with professional demand. In countries such as Sweden, Denmark, and in future the UK, where funds follow patients, it is in a hospital or local authority's interest to make sure that if a major investment is made adequate numbers of patients will follow. There is then an interest in some regional or national planning. The arguments for conforming to specialty planning on a wider basis will be balanced against the pressures from doctors and the prestige for the hospital of being associated with new developments.

As with national government involvement, hospitals and local responsible bodies are more likely to become involved when major investment decisions must be made. With procedures or smaller-scale technologies it may be easy for innovation to begin without any explicit agreement from managers.

CONSUMERS AND THE MEDIA

The main sources of information on new technologies for patients and the general public are their doctors or other health professionals, friends and relatives, consumer interest groups and the news media.

Of the three technologies in this study the one which has had the most media attention is transplantation, particularly of hearts. When Barnard undertook the first transplantation the news was relayed around the world. There is something special about the heart, with its association with emotions. Despite media interest, and perhaps because of these emotional associations, there was not a great demand from the public for diffusion of heart transplantation. It seems more that the public followed the stops and starts of transplantation as they had watched progress towards getting a person on the moon.

Kidney transplantation was rather different. In the UK, for example, where both haemodialysis and kidney transplantation are accepted technologies, but where the numbers of patients treated are low compared to other European countries, there have been TV programmes from time to time about the situation. General public concern over transplantation has been about selection criteria, for instance age discrimination, and waiting lists. However, these issues result more from organ shortage than from lack of diffusion of the procedures.

Media *influence* over transplantation has usually been mostly concerned with organ procurement. At different times and in different countries the influences have been diametrically opposed. For example, before the criterion of brain death was accepted, some of the media sensationalised stories about hearts being removed from donors declared dead too early. As a result the number of organs available for transplantation sharply declined. Brain death has been an issue in the UK and Denmark, and was only accepted in Denmark in 1990.

On the other hand, the media have also been instrumental in encouraging

donation of organs by spotlighting examples of those – children especially – waiting for organs.

The public has been involved in transplantation mostly through the media, except kidney transplantation, where associations of patients have been more active.

With stone treatment, public involvement has also been fairly low-key, and the media mostly portrayed lithotripsy as another technological miracle. Early on there were attempts by urologists to use patient power to lobby for machines. Urologists outside FRG said they were being pressured by patients for access to the treatment in Germany since it was not available in their own country. Waiting lists of patients were drawn up, for example, by the key urologist in Paris. However, as Kirchberger points out in his analysis, given that PCN was readily available as an alternative, it is not quite clear what these lists meant.

Prenatal screening differs from the others. There is a strong consumer movement associated with perinatal care and it might be expected that consumers would have more influence over diffusion. It is certainly true that the country reports describe more consumer involvement through interest groups, and more, recently, through individual patients requesting screening. Even so, the overwhelming impression is that the diffusion of amniocentesis, of MS-AFP screening and, more recently of CVS is determined by professionals rather than patients.

As with the other technologies the media played a part in informing the public about the availability of the tests. In Sweden and FRG professionals used the media quite explicitly to generate interest. In countries such as Spain and Portugal, which had repressive regimes in the early days of amniocentesis and MS-AFP screening, the restrictions on the press meant that the public were unlikely to have had much knowledge of what was possible. These countries are also the ones where the negative attitudes of many doctors to abortion meant that the public was not going to be enlightened by this source, either.

Patient–public involvement occurred most strongly in a few countries: Sweden, Denmark, UK, The Netherlands and FRG. The issues are rather different. In Sweden, the argument centred around the right to life for disabled people. This involved both the individuals themselves and parents, and although it was vehemently argued that defective fetuses should not necessarily be aborted this was not a uniform view across all groups. By contrast, in The Netherlands a group of handicapped people argued strongly for screening. In Germany, worries were based on the historic concerns about eugenics. In the FRG, feminist socialists have been most active in arguing against screening and the abortion of defective fetuses. The feminist group RotaZora planted a bomb which destroyed the genetic counselling centre at a medical school. In Denmark there was public debate around ultrasound and its safety.

Aside from organised groups there is some limited and anecdotal evidence that individual women's demands have affected diffusion. Several rapporteurs suggested that this was one reason why CVS was diffusing rapidly in their countries. In the UK, it was in trials of CVS versus amniocentesis that several

maternity interest/pressure groups became involved in helping to design trials and in providing information to women about taking part in the study. There have also been cases of patients sueing doctors because they asked for amniocentesis, were denied it and then delivered a handicapped baby.

While there is evidence that individuals and consumer groups have been active in prenatal screening, they still do not seem to have been strongly influential. This may be in part because of the conflicting views expressed by different groups. They are seldom as coherent a body as the medical profession. In some countries consumer groups have been unknown until recently, partly because of earlier press restrictions. It is also very clear that doctors are still acting as gatekeepers to these technologies, both at individual patient level and in their more general diffusion.

COMMERCIAL INTERESTS

Industry's role in the diffusion of technology is probably greater than might be suspected. For large machines such as the lithotripter, industrial interests are obvious, but even with prenatal screening a surprising amount of research funding came from commercial sources.

Taking the lithotripter first, there are two strands to the commercial interests. One concerns the interest of governments in protecting the home market for national firms, the other concerns the attempts made by industry to gain access to new markets by particular 'deals'.

Protecting national firms

Both France and Denmark in this study tried to gain time for machines to be developed in their own country. The French have a number of mechanisms available to achieve this policy: the Carte Sanitaire allows only certain numbers of items per head of population and can be used to delay diffusion; and the approvals required for the equipment itself, 'homologisation', mean that it is also possible for only certain types of machines to be approved. In Denmark these types of regulation did not exist, but the planning debates allowed a consensus to develop that machines would not be purchased until Danish machines were available.

Entering the market

It is unclear in the FRG how much of the early diffusion of ESWL was based on support for a German industry. It is known that the links between Dornier and the German Kidney Patients Association, which played a central part in the early diffusion, were extremely close. For a variety of reasons, then, the country where the lithotripter was developed remains today the one with the highest machine/population ratio.

To get a foothold in markets in particular countries the firm concerned often does 'deals' with groups of doctors or even planning authorities. In this study the most interesting example is the German firm Siemens' allowance of one year's free use of a machine by a group in Denmark, which broke the

consensus there about delaying purchase. Other arrangements about leasing, long-term loans, etc, also took place in other countries.

Prenatal screening was taken up earlier in countries where some financing from industry was available. The prenatal screening review cites three examples: the FRG where funds from a West German industry helped establish the clinical genetics programme; the UK where two firms contributed to funding the influential AFP collaborative study; and Italy where acquisition of equipment was achieved in part by charge-free loans from the manufacturing industry. More generally, research funding, sometimes from industry, was the base on which new tests could be 'piggy-backed'.

Although there is little specific evidence in the country reports it seems likely that support from the drug industry has helped take forward heart and liver transplantation programmes. There is strong mutual dependency: the industry needs transplant centres to test immunosuppressive drugs in a clinical setting, while the transplantation programmes cannot develop without these drugs.

Apart from direct finance, firms (particularly drug companies) sponsor international meetings at which ideas about new technologies are exchanged. Also, of course, industrial representatives visiting laboratories and service departments pass around the system a great deal of information about technological innovations.

EVALUATION: ITS ROLE IN THE DIFFUSION PROCESS

Some differences emerge across the three technologies and countries in the role of evaluation in the diffusion process.

For lithotripsy, it is clear that doctors were convinced both about clinical benefits and about cost-effectiveness very early on and went so far as to express the view that trials would be unethical. In several of the countries it was others, usually those responsible for investment decisions, who pressed for evaluation to be undertaken. Sweden, France, The Netherlands and UK are all known to have had considerable debates about evaluation of lithotripsy at the start of the diffusion process. In France and The Netherlands the first machines were funded on the understanding that evaluation would take place. In the event the French urologists did not provide data. In Sweden perhaps the most thorough evaluation took place through the insistence and provision of research funds by the Association of County Councils. The research included short-term treatment outcomes as well as longer-term stone recurrence rates and side effects in a comparative study against PCN, as well as a broader technology assessment. Results from these studies began to emerge in 1987 and were used for further planning decisions, although the recommendations were not fully adhered to subsequently.

In the UK the proposal from researchers to the Department of Health that there should be a randomised controlled trial (RCT) of lithotripsy against other forms of stone treatment was strongly resisted by urologists. In the end all that was acceptable was a descriptive comparative study. Even this brought out a number of questions about the cost-effectiveness of lithotripsy versus PCN for different patient groups. The results have been criticised because they do

not have the scientific rigour of an RCT! However, with gallstone lithotripsy there appears to be less conviction that the answers are clearcut and an RCT comparing lithotripsy with percutaneous treatments has been possible.

This differs considerably from evaluation discussions in prenatal screening. Although randomised controlled trials were not undertaken in the early stages of development of amniocentesis, the individuals responsible did carry out studies of risk of fetal loss. An RCT was subsequently done in Denmark. More recently there have been trials of amniocentesis versus chorionic villus sampling led by the professional groups and researchers involved in perinatal care and not by governments. Not all involved in CVS are convinced of the need for trials, however. The intention was to conduct trials using common protocols across a number of countries. This did not work out in practice, but the UK did go ahead with an RCT involving participants in Denmark, Italy and The Netherlands. Government and funding bodies have played a very minor role in evaluation. For MS-AFP screening large-scale collaborative studies in Sweden and the UK were undertaken to establish the risks and benefits of screening. These were funded from a variety of sources, both charitable and commercial.

In the studies mentioned, governments did of course pay a great deal of attention to the results. This was particularly so for MS-AFP screening, where a number of countries set up national working parties to advise on whether there should be a national screening programme.

Liver and heart transplantation lie somewhere intermediate between the two examples. The procedures were perceived as being expensive, and it was in the interests of the early innovators to collaborate with governments and funding bodies on evaluation. Individual clinician responses will clearly not be uniform, but there seems to have been reasonable agreement in the UK with the Department of Health about the need for a study of outcomes in terms of quality of life and of costs for heart transplantation. It is unclear how much influence the resultant study had. It gave a more positive view of the cost-effectiveness of heart transplantation than had perhaps been expected, and two centres were funded. Buxton argues[5] that policy followed behind local decisions rather than determining events. However, the evaluation probably influenced the spread and speed of introduction of heart transplantation.

Similarly, in The Netherlands the lead for evaluation came from the Sickness Fund and Health Councils. The Academic Hospital Groningen had already started a liver transplantation programme and the Academic Hospitals of Rotterdam and Leiden cooperatively had started heart transplantation. Thus the assessments were in effect imposed on them as a condition for funding these activities. The assessments were broad and the final reports in 1988 influenced the decisions of the Sickness Fund Council: to include heart transplantation in the set of insured care provisions but not to do so at that time for liver transplantation.

A number of other countries set up working groups to assess heart and liver transplantation but the only other countries to undertake anything approaching a full evaluation were Sweden and the USA. The US heart study, and particularly the US consensus conference on liver transplantation, were quite influential in discussions in various European countries.

Other literature,[6] including a study of randomised controlled trials by the US Office of Technology Assessment,[7] has shown remarkably little influence of trials on the initial diffusion of medical technology. In these studies RCTs, if established at all, took place rather late in the diffusion process. This is less the case with the technologies in this EC study, especially transplantation. For lithotripsy, trials were opposed by the doctors concerned on the basis of the self-evident improvement of care. Consequently there is less information than there should be about which treatments are appropriate for which groups of patients, especially when the long-term effects are considered. Governments, it appears, did not press heavily for evidence. For prenatal screening the lead has been taken by the professional groups and the results of clinical trials and cost-effectiveness studies do seem to have influenced the arguments and the practices, though not necessarily in a uniform way. For transplantation a number of governments/funding bodies have insisted on good studies as a basis for making funding decisions and doctors seem to have been willing to support the need for assessment. The effects of the results on policies and the diffusion pattern are less easy to determine, but certainly seem to have been influential in The Netherlands and Sweden.

The more southerly European countries have less of a tradition of evaluation research but have tended to draw on the results of studies from other countries. There is no information on how much trial evidence has been taken into account in decisions.

6 CONCLUSIONS

Three conclusions emerge quite clearly from this study: that the medical profession, as individuals and as a group, has been the dominant influence over the introduction and diffusion of these medical technologies; that the role of the consumer has been surprisingly weak considering that several of the technologies involved major ethical issues about life, death, and disability; and that in no country in this study was full central or governmental control over all the technologies attempted or achieved, though The Netherlands and Sweden stand out as having gone further in this respect than others. Even accepting that the diffusion of medical technology will never be an entirely rational process, there are several ways in which it could be improved.

Educating the medical profession

Given that doctors are the key actors in the process it is clear that little will change unless they accept the need for evaluation of new medical technologies to be built into undergraduate and postgraduate training. There is some evidence of a move to make medical education less fact-driven and to emphasise more 'learning how to learn'. The issue of scientific evaluation could be accommodated more easily under that scenario.

Even if better training were instituted immediately, such understanding would take time to become evident in the system. There is a need to develop the understanding of doctors in practice now. There is no easy route, but governments could work with the relevant professional bodies in each country to persuade them to take a lead. Because of the different health systems in EC countries and the way that doctors are financed, the precise mechanisms to be used to influence and educate doctors will have to be determined locally.

The major concern that doctors share when evaluation or technology assessment is discussed is that patients may be denied benefits during the evaluation period. Doctors need to be persuaded that it is worth some delay to ensure that health care resources are not wasted and that current and future patients receive appropriate treatment based on good evidence and not on unproven assumptions. But there is a challenge in this both to the governments concerned and the researchers undertaking evaluations. The evaluations need to be undertaken as speedily and conclusively as possible. Methodologies need to be improved so that early outcomes can lead to some early decisions as part of a gradual process.

Another concern is that innovation will be stifled and that scientific brilliance cannot be turned to national account. However, this is more of an issue about early support for the development of new ideas rather than an argument about good evaluation of emerging technologies.

Government's role

If doctors are to be helped to become more critical and to call for scientific evidence in the interests of their patients, governments and national financing

bodies will also have to show that they are serious about these issues. A strong sense came out of this study that governments would prefer not to have to intervene in medical issues but to leave it to the medical and related professions.

What seems to be necessary is for governments to be clearer about which technologies are emerging, which of them will require their attention, and which can be left to be 'managed' within the medical profession. The Netherlands have taken the lead with this approach with their Steering Committee on Future Health Scenarios.[8] The next step is to make sure that appropriate evaluations are undertaken. Often with the 'big ticket' technologies governments are in a position to insist that evaluations are done before initial introduction takes place. The regulation is wider, subsequent diffusion is more complex and, as described above, different countries have different policy levers they can use. Individual regulation of specific technologies has not been a very effective control mechanism, however, partly because it is subject to too many loopholes or abuses. More control seems to have been achieved where there is some commitment to regional planning. The acceptance of that approach at local levels may be strongly influenced by a realisation of the financial risks and penalties incurred by not adhering to the agreements.

As described in the earlier EC study,[1] budgetary constraints do work, but they can be a fairly heavy-handed control mechanism. It is no use keeping every innovation dampened down and not discriminating between those that have been proved effective and those that are unevaluated. Of course, there is no doubt that global budgets do make people think more carefully and a number of countries are moving in that direction; but better technology assessment information is essential for local decision makers if they are to assess trade-offs in the care they are providing within those local global budgets.

In The Netherlands and Sweden the introduction and use of medical technology appears to be somewhat more successfully controlled. The combination of three key factors makes this possible: acceptance of government's role in ensuring that technology assessments are undertaken; willingness of governments to use the policy levers which are available to them; and recognition by those at local levels of the need for controls and perhaps broad planning agreements.

Involving the consumer

The third issue is the role of the consumer. Some of the EC countries, especially those which have or have had tight controls over the press, have very little tradition of consumer involvement in health care. However, even in northern European countries, where consumerism is said to be strong, little evidence emerged of real influence over these medical technologies. In this study Denmark appeared to have gone furthest in exposing issues to public debate and public influence.

If it is believed that many medical technologies have such significant social and cost implications that the public does have a legitimate interest in their diffusion, how can its role be fostered?

The weakness of consumer groups in comparison to the power and greater organisation of the medical profession implies the need for some lead from governments if consumer groups are to be taken seriously. As in Denmark, there needs to be a positive move to open out issues to the public and to invite consumer groups into the medical and political settings where decisions are being made. An underlying requirement is that medical issues are explained in such a way that patients, consumer groups and the public can begin to understand what the issues and uncertainties are about. This is by no means impossible. Public consensus development conferences in Denmark, the UK and elsewhere have shown such explanation to be quite feasible. It does, however, require a willingness on the part of the medical profession to do so, and it is governments and other national policy bodies that will probably have to take the lead and set an example.

Overall then there is a clear if difficult agenda for action for policy makers and other leaders across Europe if technologies are to be introduced and used more appropriately in our health care systems. While the agenda is common, the approaches and solutions which are suitable for different EC countries will be quite varied. Nevertheless, there is a great deal to be learnt from each other as countries begin to move forward on these issues.

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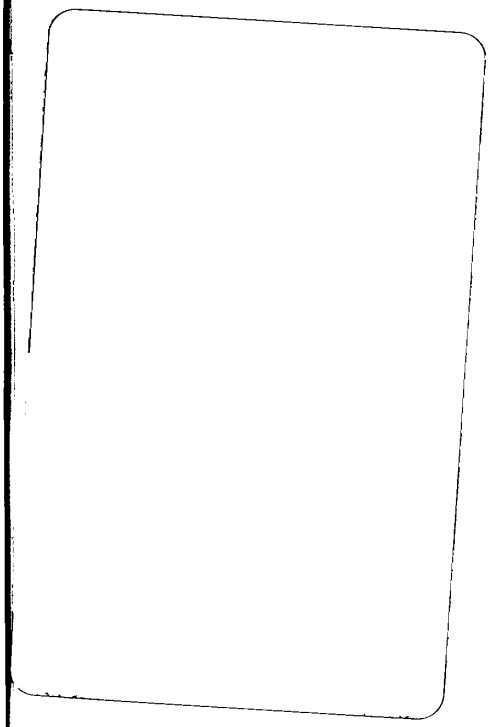

Medical technology, defined broadly to include drugs, procedures and equipment used singly or in combination, has been of enormous benefit in improving the quality of health care. It has, however, raised many issues about how society can afford to pay for these often expensive developments and about associated ethical problems and social impact. This book, one of three dealing with different medical technologies, is about the effect of these issues on the rate of diffusion of these technologies in the countries of the European Community and Sweden, from the time of their introduction up to 1990. It is based on first-hand reports from informed observers of the health care scene in each country.

The three technologies are: prenatal screening for metabolic or anatomical disorders, especially Down's syndrome and neural tube defect; treatment of kidney stones by lithotripsy and/or endourological procedures; and kidney, heart and liver transplantation, with the attendant problems of organ donation and procurement. The influence of ideas of technology assessment, recently introduced in some countries, is critically examined at the end of each volume.

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