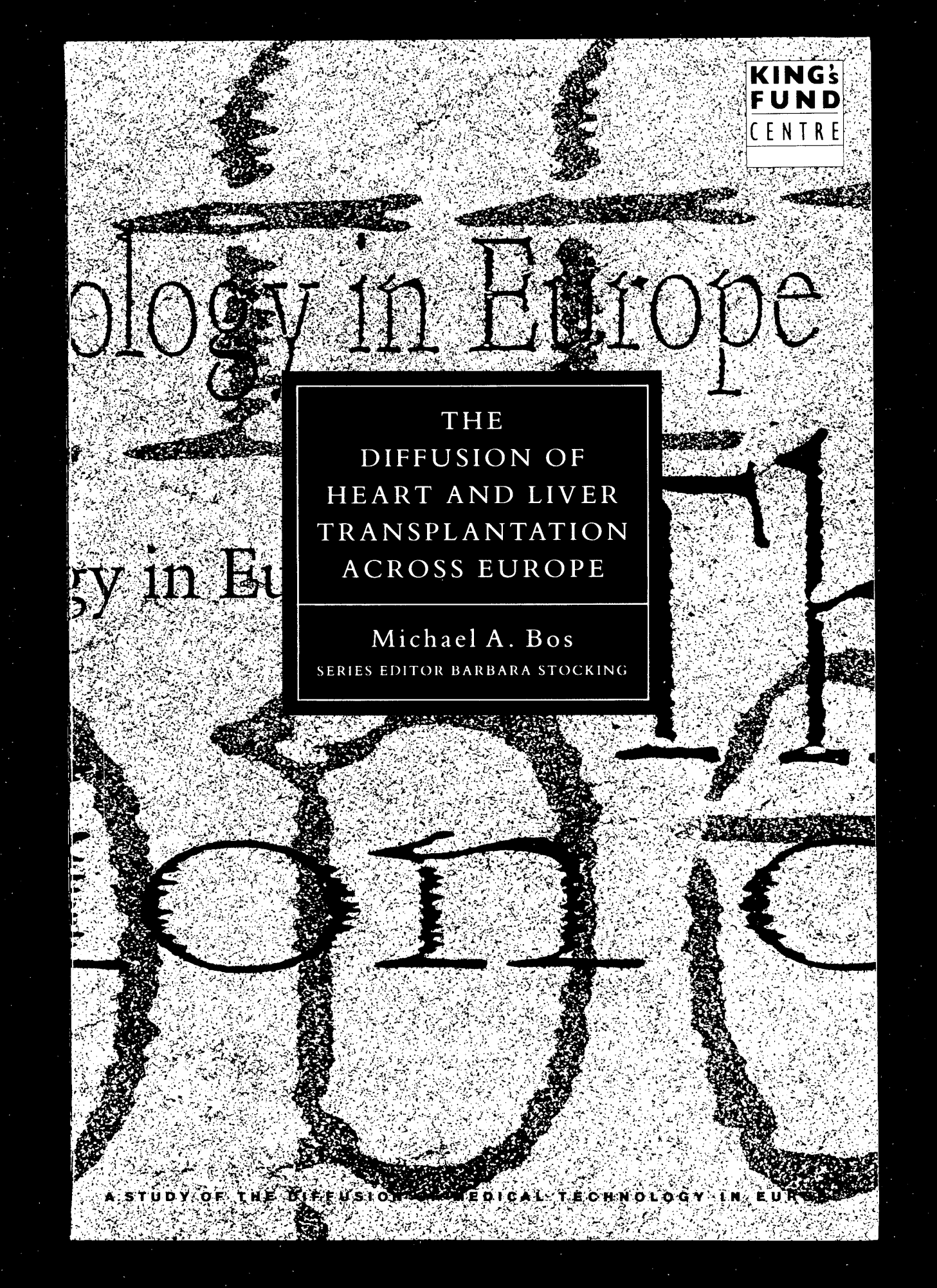
KING's FUND CENTRE
THE DIFFUSION OF HEART AND LIVER TRANSPLANTATION ACROSS EUROPE
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SERIES EDITOR BARBARA STOCKING

A STUDY OF THE DIFFUSION OF MEDICAL TECHNOLOGY IN EUROPE

THE DIFFUSION OF HEART AND LIVER TRANSPLANTATION ACROSS EUROPE

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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

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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.

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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 EC 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 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. Stefan Kirchberger 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

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FOREWORD AND ACKNOWLEDGEMENTS

There has been serious experimentation with organ transplantation since the beginning of the twentieth century, but only in the past thirty years has kidney transplantation using unrelated donors become clinically feasible and only in the past twenty have heart and liver transplantation become accepted, and then only in some countries. Adoption of the techniques raises formidable financial, organisational and ethical questions which have been addressed differently in different European countries. A consideration of these differences is enlightening.

Data on which this review is based derive mainly from reports received from all the EC countries and from Sweden, which was included as a participant in the EC COST (Coopération Scientifique et Technologique) programme, plus reports from countries outside the EEC, listed with their rapporteurs below.

Belgium: Prof Dr Guy Alexandre, Université Catholique de Louvain, Clinique Universitaire de St Luc, Transplant Unit, 10 Ave Hippocrate, 1200 Bruxelles

Denmark: Dr Bo Andersen, Danish Hospital Institute, Nyropsgade 18, 1602 Copenhagen

France: Dr Catherine Viens-Bitker and Dr Pierre Durieux, Assistance Publique de Paris, 3 Ave Victoria, 75100 Paris RP

Germany: Prof Dr Rudolf Pichlmayr and Prof Dr H G Borst, Medizinische Hochschule Hannover, Klinik für Abdominal u Transplantationschirurgie, Konstanty Gutschowstr 8, 3000 Hannover 61 and **Prof Dr Harald Lange,** Universitätsklinikum Lahnberge, Zentrum für Innere Medizin, Baldingerstrasse, 3550 Marburg/Lahn

Greece: Dr Maria Varla-Leftherioti, Hellas Transplant Service, General Hospital of Athens, 144 Messogion Avenue, 115 27 Athens

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Italy: Prof dr Girolamo Sirchia, Centro Trasfusionale e di Immunologia dei Trapanti, Ospedale Maggiore di Milano, Via Francesco Sforza 35, Milano

Luxembourg: Dr Elisabeth Heisbourg, Division de la Médicine Curative, Rue Auguste Lumière 4, L-1950 Luxembourg

The Netherlands: Dr Frank de Charro, Faculty of Law, Erasmus University, Postbus 1738, 3000 DR Rotterdam and **Bernard Cohen** and **Dr Guido Persijn,** Eurotransplant Foundation, University Hospital, PO Box 9600, 2300 RC Leiden

Portugal: Dr Joao Queiroz e Melo, Hospital de Santa Cruz, Ave Prof Reinaldo dos Santos, Carnaxide, 2795 Linda-a-Velha

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Finland: Dr Jari Kankaanpää, Helsinki University of Technology, Institute of Biomedical Engineering, Rakentajanaukio 2C, SF-02150 Espoo

Norway: Dr Dagfinn Albrechtsen, Rikshospitalet University Hospital, Surgical Dept B, 0027 Oslo 1

Switzerland: Prof dr R Megevand and **Dr M Jeannet,** Unité d'Immunologie et de Transplantation, Hôpital Cantonal, Rue Micheli-du-Crest 24, 1211 Genève.

The country reports given in this volume were selected to illustrate some of the specific influences on the diffusion of organ transplantation and the associated organ procurement. Reports are included from the The Netherlands, the UK and Greece.

The *Dutch* report demonstrates a centralised series of decisions concerning heart and liver transplantation. Early decisions were taken to subject heart and liver transplantation to separate technology assessments, and while these were undertaken the preliminary programmes were funded under special arrangements and not as regular health care provision. Only after the results became available did decision-making bodies consider regular provision.

The *United Kingdom* report emphasises the issue of the availability of organs for donation and the requirement that hearts and livers be removed from heart-beating donors. This required the acceptance of brain death criteria and led to much public debate. The UK report also illustrates how concerns about costs also were a brake on the rapid diffusion of these procedures and like The Netherlands, there was considerable involvement by central government in the diffusion process.

Greece is at a rather different stage in the diffusion process, in that heart and liver transplantation have been introduced there only very recently. Major effort is being put into heightening awareness of organ donation on the part of the general public, and as yet there has been no controversy over brain death.

1 INTRODUCTION AND SUMMARY

Although the grafting of kidneys, hearts and livers has become a clinical reality only in the last 30 years it is no longer considered exceptional, but a routine – albeit demanding – procedure. At the same time it is true to say that, considering the rate of development, both scientific and clinical, organ transplantation is still in its infancy. We can be almost sure that this field will undergo many further changes and developments, including the following:

- new grafting procedures will be tried;
- other organs and tissues will be transplanted;
- more effective immunosuppressive treatment will be developed;
- better preservation techniques will be found.

Although in some ways organ transplantation is no different from other dynamic sectors of medicine (eg molecular biology treatment in cancer, DNA testing for genetic defects), there are significant differences. Firstly, however the procedures may be refined, organ transplantations cannot be performed in infinite numbers, as there is a limited supply of human organs, whether from living or deceased donors. Human organs must be considered 'scarce national resources'. And this will probably remain so for the foreseeable future.

Other important, but not unique, characteristics of organ transplantation are that:

- it takes place in a highly emotionally charged context: (usually) death of the donor, consent by the family, selection of recipients and waiting lists
- transplantation is often a directly life-saving procedure
- transplantation touches on the question of the limits to medicine – technical and scientific, but also social and ethical
- transplantation is not only a benefit, but also, to some extent, a burden to the recipient: he or she is often condemned to life-long drug treatment and can never be considered a completely healthy, normal person
- transplantation is at present a very costly form of treatment that competes with other priorities in the community and the health care system.

Although the volume of organ transplants is small when compared to the number of patients with cancer, diabetes or heart and vascular diseases, much attention is concentrated on this form of treatment. And society is prepared to spend vast sums of money on it – sometimes up to $500,000 for a single patient – although the gain, relative to the total burden of disease to society, is modest. Few communities have made the same choice as the Oregon State (USA) authorities, which have virtually stopped organ transplants in favour of other health care priorities.[1]

The media have also devoted much attention to organ transplants, both because of their dramatic life-saving potential but also because of negative aspects such as commercialisation and aggressive organ procurement policies. All this has made transplantation one of the widest known medical procedures among the general public.

[1] References, p 102.

Organ transplantation has become a generally accepted procedure, with a good prognosis for most organs, and it is practised in a great number of countries in Europe, North America and the developing world. It is, therefore, interesting to find that there are significant differences, even in western Europe, in the way that countries have adopted and use transplantation technology. Some EC countries are amongst the world's pioneers in transplantation, while others have only recently introduced some of these procedures to their health care system. A few countries have tried or managed to influence the introduction and diffusion of transplantation technology, while others have left this to the forces of the health care 'market'.

It is our aim here to explain the differences and to describe the different regulatory mechanisms at work. The rest of this chapter summarises the study's major observations and conclusions.

The *development of organ transplantation* has a history dating back to the beginning of the twentieth century, when experiments with surgical techniques and grafting in animals started in France and the USA. However, it took 50 more years before the technical and immunological problems had been overcome to the extent that organ grafting could become a clinical reality. The most important breakthroughs were the development of immunosuppressive therapy, the unravelling of the histocompatibility system and the development of techniques for preserving ischaemic organs. Kidney transplantation started with the use of organs from genetically related, living donors, but soon the technique for accurate tissue matching made the use of unrelated cadaveric donors possible. The growing need for cadaveric organs led to the development of organisational infrastructures that could deal with organ procurement, tissue typing, and matching and exchanging organs on a national scale. Also, most countries adopted legislation regulating or regularising the procurement and use of organs for therapeutic purposes.

Kidney transplantation in Europe diffused more slowly than in the USA for two reasons. One is that in most European countries the use of living donors is not advocated, while in the USA it makes up almost 25 per cent of all transplants. The second is that organ procurement in the USA was well organised as early as 1974, and the US health care authorities were financially supporting the programme, whereas in a large part of Europe (with the exception of Scandinavia and the Eurotransplant countries) kidney transplant programmes were rather weak and developed slowly. For 1988 the number of kidney transplants per million population (pmp) in the USA was almost 40, while in Europe as a whole it totalled 24. However, it looks as though the USA has reached a ceiling for the moment, whereas transplantation in Europe continues to grow. The number of transplants performed in European countries ranges from fewer than 15 pmp (Italy, Greece and Turkey) to 40 pmp (Belgium, Scandinavia, and Austria).

Heart and liver transplantation developed on the basis of the experience gained in kidney transplantation. They also profited from the existence of an infrastructure for organ procurement that was already in place. In the USA the clinical development of heart and liver transplantation took place earlier than in Europe, with at least five years' difference between them. However,

at the beginning of the 1990s Europe is quickly catching up.

In Europe the countries that pioneered heart and liver transplantation (1968–80) were France, the UK, FRG and Belgium. Countries in the south of Europe started 5–10 years later. The last countries to start heart and liver transplants were Denmark, Greece and Turkey: this was due to a lack of infrastructure (Greece and Turkey) or to the fact that brain-death criteria were not accepted (Denmark).

There is still a great potential for growth of organ transplants (kidney, heart and liver) in Europe, since a number of countries have started late and in most countries there is scope for an increase in the number of organ donors (fewer than half the available donors are used). At the same time, waiting-lists for organ transplants are rapidly increasing everywhere, creating allocation problems.

A large number of factors affect the rate of diffusion of transplant programmes. We have looked into the following.

Role of the medical profession

No organ transplant programme could have started without the presence of scientifically interested, ambitious and enterprising individuals, backed by centres of medical excellence. Medical doctors (surgeons, nephrologists, cardiologists, hepatologists, immunologists) were the driving forces behind the diffusion of transplantation.

Infrastructure in organ procurement and exchange

The diffusion of kidney transplantation and the introduction of heart and liver transplantation were only possible in situations where organisational arrangements for procurement and exchange of donor organs had been made. The first organisation of this kind in Europe was Eurotransplant (1967). Nowadays, all European countries have exchange agencies operating on a regional, national or international scale.

Legislation on organ procurement and donation

Procurement of cadaveric donor organs on a large scale is possible only when legal protection is given to donors, and the rights and duties of all concerned have been clearly spelled out. Specific legislation has now been adopted in almost all European countries (14 out of 18 studied in this report). Most countries have adopted the 'opting-out' or 'presumed consent' principle in their legislation. Recently, the international organisations (WHO, Council of Europe and the EC) have been active in harmonising legislation and regulation concerning organ transplantation in the member states.

Role of health authorities

In most countries neither the health authorities nor the health care financing agencies played an important role in the introduction and early diffusion

of organ transplantation. Although in a number of countries instruments for regulation were available to the government (central or regional), these were seldom applied to organ transplantation. Most countries regulate expensive medical devices and equipment. Only The Netherlands and the Scandinavian countries have planned the diffusion of organ transplantation to some extent. In other countries, indirect control has been exerted through the allocation of tight budgets. In most countries the financing agencies (national health service or public and private insurance agencies) have reimbursed organ transplants from the start. In later years, since cost-containment policies have become a dominant feature of health care policy, the health care agencies have become increasingly interested in regulating organ transplantation, examining both quality and cost-effectiveness.

Role of the media

The media have certainly played a role in the diffusion of organ transplantation: their involvement has been both negative and positive. In a positive sense they have contributed to the education of the public concerning transplantation, enhancing the willingness of the public to donate organs. But there also is ample evidence that sensational (and even irresponsible) reporting on the darker sides of transplantation, such as commercial activities and uncertainty over brain-death criteria, have been detrimental to its acceptance.

Effect of assessment studies

Technology assessment studies in medicine have in recent years become useful tools for decision-making and planning in health care policy. However, assessment studies in organ transplantation have been few, up till now, and their effect has been relatively slight. Most assessments have been done in Scandinavia, The Netherlands and the UK.

2 A SHORT HISTORY OF ORGAN TRANSPLANTATION

The idea of replacing damaged, non-functioning human organs by substitutes may be as old as medicine itself. However, the exact origin and date of this procedure are lost and its development is obscured by mythological tales. Early Chinese medical history has recorded the miracles performed by doctor Pien Xiao, who is reputed to have exchanged the hearts of two human beings in the second century BC. In Europe a number of mediaeval paintings depict the scene of Saints Cosmas and Damianus transplanting the leg of a Moor to a wounded crusader, a feat that is said to have taken place in the fourth century AD.

However, if we look for well-documented, scientific achievements and developments, organ transplantation appears to be a rather young branch on the tree of medicine. The foundations for the surgical skills and the biological understanding that are necessary to perform successful grafting of human organs were laid at the beginning of this century; clinical transplantation of vital organs in humans started a mere 35 years ago.

THE DEVELOPMENT OF BASIC SKILLS IN TRANSPLANTATION

One can identify the collaboration between Alexis Carrel, a French surgeon, and David Guthrie, an American physician, as the starting point of modern transplant medicine. Carrel had specialised in vascular surgery and in 1901 succeeded in successfully rejoining the veins and arteries of an animal thyroid gland. Once this technique of *anastomosis* had been developed and refined, Carrel and Guthrie started to work together at the Hull Physiological Laboratory in Chicago, where they explored the transplantation of all kinds of organs and tissues in animal models. In 1904 they performed a kidney transplantation in a dog, and by 1905 experimented with cardiac transplantation, also in dogs.

Although after 1905 Carrel left for the Rockefeller Institute in New York and Guthrie moved to Washington University in St Louis, they kept up their collaboration in animal organ grafting and published their early findings.[2] These publications are now considered landmark articles in transplantation, but they went largely unnoticed by the leading surgeons of the day.

By 1910 Carrel, now working alone, summarised his work on kidney transplantation in a new article[3] in the *Journal of Experimental Medicine*, where he focused on the contrast between allografts and autografts. It is clear that Carrel already foresaw the possible consequences of his findings for transplantation in humans. Thus the procedures of kidney and heart transplantation, as performed by Carrel and Guthrie, can be regarded as prototypes of today's transplants.

Another landmark discovery at the beginning of this century was the work of Landsteiner, an Austrian scientist who reported in 1901 on red blood cell antigens and their individual specificity.[4] With this he laid the foundations of immunology – a field that was to become a central issue in transplantation. The years between 1930 and 1940 brought better insight into the importance

of blood group compatibility and the meaning of cold ischaemia time for the viability of animal organs used in experiments. This led to the development of preservation fluids for organs.

However, the greatest step forward at this time was achieved through the work of Peter Medawar, an Oxford zoologist. Working with the plastic surgeon Percy Gibson he studied the rejection reactions in skin grafts, performed on burn victims. Medawar concluded that the rejection of new, grafted tissue was a response of the recipient's immune system. In animal studies it was further shown that this response became stronger with repeated grafts. In cooperation with the biologist Rupert Billingham and the immunologist Leslie Brent, Medawar arrived at the conclusion that the immune response, as induced in animal experiments, was not present in genetically closely related species. This led to the theory of 'acquired tolerance'.[5]

They succeeded in finding ways to manipulate the immune response in animals, inducing immunological tolerance in genetically distinct tissues, and thus making it possible to transplant cellular tissue across histological barriers. With publication of Medawar's work in 1953 the cornerstone was laid for the development of immunosuppressive therapy, which proved to be of crucial importance for human organ transplantation.

In the early 1950s the development of surgical skills and the progress in understanding the human immune system had given doctors the confidence to try clinical transplantation of a vital organ in man, cornea transplantation having by that time already become a successful procedure. The first experiments with kidney transplants between genetically related donors and recipients showed that kidneys from related donors were more compatible than organs from non-relatives and 'inborn tolerance' (Medawar) contributed to graft survival. Relatedness was not sufficient to suppress the human immune response entirely. Only in a renal transplant between identical twins was rejection absent; otherwise, rejection appeared to be the key stumbling block.

The observations of Medawar and their own early and unsuccessful experiences in renal transplantation stimulated two French scientists, the immunologist Jean Dausset and the nephrologist Jean Hamburger, both working in the Hôpital Necker in Paris, to look for identical genetic markers in unrelated persons that could be used as indicators for enhanced immunological tolerance. In 1958 Dausset, while studying the reactions between antigens and antibodies, discovered a leukocyte antigen that he thought might be responsible for graft rejection.[6,7] This led eventually to the discovery of human leukocyte antigens (HLA) on chromosome 6. These findings triggered off the development of the HLA system as a basis for tissue typing and matching, and this in turn became the basis for immunologic selection and matching of organ donors and recipients.

In later years the HLA system, which showed itself to be enormously polymorphic, has been refined and made usable for routine clinical transplantation through the work of Jon van Rood, a Dutch immunologist.[8] He later advocated the idea of matching cadaveric donor kidneys to recipients on a European scale, from which sprang (1967) the Eurotransplant organisation, the first organ exchange programme of its kind in the world.

THE SEARCH FOR IMMUNOSUPPRESSIVE THERAPIES

Although, as we have seen, progress in surgical technique and the ability to match donor and recipient on the basis of tissue similarity (histocompatibility) were of vital importance to clinical organ transplantation, this proved in most cases insufficient to circumvent the complexities of the human immune system. More effective suppression of the immune response would have to be accomplished before organ transplanting could become a feasible, let alone routine, procedure.

Already in 1959, experimental work in rabbits by Schwartz and Dameshek in Boston had led to the discovery that immunological tolerance could be induced by the drug 6-mercaptopurine.[9,10] Roy Calne, a British surgeon, used this drug in his experimental kidney transplants in dogs and found that rejection did not occur in the transplanted animals.[11] These observations, made in 1960, signalled the start of the development of effective immuno-suppressive drugs. Mercaptopurine, azathioprine (Immuran) and prednisone became the ingredients of an wide variety of immuno-suppressive regimens (double and triple cocktails), which proved to be effective against rejection but not without painful and sometimes dangerous side effects. From 1966 ALG (antilymphocyte globulin) became available and proved to be a useful addition to immunosuppressive therapy. Although by 1970 organ trans-plantation, especially kidney transplantation, had become more successful because of the tissue typing and matching and through the development of immunosuppressive therapy, it had by no means become an easy and safe procedure. This was mainly because all these drugs had toxic side-effects, and they had to be taken 'for life' after transplantation.

The risks were further increased by the fact that the drugs used were polyclonal (ie procured from different cells), and therefore difficult to target on the human immune system. This problem could be surmounted only by using high doses, which often resulted in organ damage in transplanted persons. One solution to this problem was the discovery in 1975 of mono-clonal antibodies, that is identical cells produced from a single cell. This led to the development of antibodies that could be aimed at specific immune cells, such as OKT-3, an antibody that attacks only the T lymphocytes that resist foreign tissue. OKT-3 was approved for clinical use in 1986 and found to be very useful in combating sudden, acute rejection episodes in transplanted patients. However, OKT-3 was unsuitable as a drug for lifelong immuno-suppressive treatment because of its aggressive nature.

The real, long-awaited breakthrough came with the discovery and devel-opment of cyclosporin. This is a metabolite originally extracted from a fungus found in the deserted Norwegian tundra. Through a chain of seren-dipitous events the biologist Jean-François Borel, working with the Swiss chemical company Sandoz, found that a polypeptide derived from the fungus suppressed the immune system of mice by slowing down the action of the lymphocytes, but without killing them. Further experiments showed that the metabolite was able to sabotage a whole range of immune responses, but that this did not result in permanent damage to the immune system, since withdrawing the drug resulted in return of the immune response.[12–15]

In 1976 Borel revealed his findings to the transplant community, which reacted promptly. The Cambridge transplant surgeon Roy Calne used the drug in his experiments with heart transplants in pigs, was very excited by the improved survival results,[16,17] and in 1978 found the courage to use cyclosporin in human kidney transplanting. The first results were, however, disappointing because of a distressingly high rate of side effects, sometimes resulting in death of the patient. This almost spelled the end of the new immunosuppressive drug. However, when a refined version of the drug, cyclosporin A, became available, most of the problems of toxicity were resolved or reduced to acceptable proportions.

In 1983 cyclosporin A was approved for general use in the USA by the FDA and became widely available under its trade name *Sandimmune*. Its introduction effected a revolution in transplantation medicine, and is now used routinely in combination with other immunosuppressive drugs, such as steroids and azathioprine (triple therapy). This allows the use of much lower doses, which greatly reduces the adverse side effects and makes it usable in a lifelong regimen.

However, the success of cyclosporin A does not mean that all problems of immunosuppression have been solved: there are still side effects such as toxicity to the kidneys and the risk of inducing cancer. This means that blood levels of the drug must be monitored at all times. Last but not least the cyclosporin is expensive, costing as much as £4000 a year per patient. All this results in a continued search for the 'perfect immunosuppressant'.

3 THE DEVELOPMENT OF KIDNEY TRANSPLANTATION

During the development of kidney transplantation, several crucial questions have been solved, among them the search for immunosuppressive drugs, the matching of donor and recipient organs on the basis of tissue typing, and the development of organ preservation fluids. At the same time the whole organisation and infrastructure for the procurement of cadaveric donor organs was created, centres for tissue typing were established, and legislation and public awareness campaigns brought the idea of organ donation and transplantation nearer to the public. The development of kidney transplantation serves therefore as a prototype, a model of the rise and diffusion of a technology, to which heart and liver transplantation may be compared.

Only 45 years ago end-stage renal disease (ESRD), or the irreversible insufficiency of the kidney function, was a lethal condition for which no treatment was available. This changed dramatically with the invention, in 1943, of the artificial kidney by Willem Kolff, a Dutch physician and engineer. The device became the basis for the development of haemodialysis treatment, which sustains the life of over 90,000 people in the United States and some 65,000 in the EC (1987 figures).[18]

To those with total kidney failure, dialysis restores health and offers improved quality of life. But the patient is highly dependent on the technology, and the regime of two or three treatments a week is burdensome. In young children there is a risk of retarded growth and development. And the costs to the health care system rise dramatically: since 1974 in the USA, from about $229 million to an estimated $1.8 billion in 1983, the average annual increase being more than 30 per cent.[18]

In the early 1950s clinical transplantation of kidneys began in earnest with organs from living related donors, the first being a transplantation between twins. Soon it became clear that there were not enough organs from living donors to supply transplantation to those with ESRD. The rapid development of immunosuppressive drugs and the technique of tissue typing and donor-recipient matching made the use of cadaveric donor organs possible. This in turn requires patients to wait for a suitable organ, and dialysis support makes it possible for them to do so. At the same time, the transplantation of these patients with cadaveric donor organs requires an effective organisation of donor organ procurement.

THE HISTORY OF KIDNEY TRANSPLANTATION

The earliest recorded attempt at renal transplantation was the experiment by Ullmann in Vienna, who in 1902 demonstrated a goat into whose neck region the kidney of a dog had been transplanted. The kidney seemed to be functioning normally, with urine flowing in drops from a protruding ureter.[20,21] In 1906 Jaboulay anastomosed animal kidneys into an artery and vein in the arms of several patients, where they functioned for about one hour.[22]

In 1910 Carrel remarked on the differences in survival in his experiments (from 1904 onwards) between allografts and autografts:

> 'Should an organ, extirpated from an animal and replaced into its owner by a certain technique, continue to function normally, but should it cease to function when transplanted into another animal by the same technique, the physiological disturbance could not be considered as brought about by the surgical factors. The change undergone by the organ would be due to the influence of the host, that is, biological factors.'

Other early experiments in which animal kidneys were grafted in uraemic patients were carried out by Unger (1910)[23], Morel and Papin (1913)[24] and Neuhof (1923)[25], all of which were unsuccessful.

Attempts by Voronoy (1936)[26], Lundsteiner and Hufnagel (1945)[27], Lawler in Chicago (1950)[28,29], and Servelle[30], Dubost[31] and Kuss[32] in Paris were all partially successful but all eventually ended in rejection and death of the patient.

At about the same time, in the United States, several attempts at clinical kidney transplantation were made in the Peter Bent Brigham Hospital in Boston, where surgeon David Hume used kidneys from deceased but healthy people and also from living patients from whom a kidney had to be removed because of illness.[33,34] In all these transplants the kidneys initially started to function, and the uraemia was reversed for a while, but inevitably rejection occurred and the patients died. In the years 1951–3 ten kidney transplants were performed in this way.

Meanwhile Hamburger had successfully transplanted a kidney from a living, genetically related donor into a patient who had ruptured his kidney in an accident. Rejection set in after 22 days.[35] The most successful transplant to date in 1953 was performed by Hume in Boston; the patient left the hospital with a functioning kidney after 81 days, but after six months died suddenly from renal failure.[36]

By this time it had become clear that all the 36 or so reported transplants using cadaveric or 'free' kidneys had eventually failed because of rejection by the recipient's immune system. The only possible solution to successful renal transplantation lay, it was realised, in the effective suppression of the human immune response.

However, it was also recognised that there may exist a single situation where immune responses could be 'tricked': this was in the case where transplantation took place between monozygotic twins. This phenomenon had already been observed in 1939 by Brown, when he was performing skin grafts. And so on 23 December 1954, Murray and Merrill in Boston performed the first renal transplantation between identical twins.[37] The operation was highly successful and was followed by an uncomplicated healthy life of eight years, when the patient suddenly died of myocardial infarction.

Soon after this event there followed the first successful kidney transplantation in Europe, when in 1955 the Paris group gave a patient a kidney from a living donor. In the late 1950s and the early 1960s the first effective immunosuppressive drug (6-mercaptopurine) was developed by Schwartz and Dameshek. This finally made possible successful kidney transplantation from deceased, genetically unrelated donors. The first of the transplants was

successfully carried out by Murray in Boston, soon followed by Woodruff in Edinburgh in 1962. Both made use of the recently developed immunosuppressants and of the knowledge of histocompatibility (Dausset's discovery of HLA was in 1958).

Thus, the development of kidney transplantation from animal experiment to clinical reality in humans took 50 years to become 'mature'.

Kidney transplantation first succeeded through the use of living, genetically related donors to circumvent the problem of rejection by the immune system. However, as soon as the immunosuppressive 'hurdle' had been surmounted, the emphasis shifted to the use of cadaveric donor organs, making possible the enormous increase in the number of transplantations world-wide. But the use of living related donors has never stopped completely and is now again under discussion as a possible solution to the ever-increasing shortage of donor organs.

THE RESULTS OF KIDNEY TRANSPLANTATION

The results of kidney transplantation, judged by graft and patient survival data, have improved very significantly over the years in transplant centres all over the world. A really significant improvement was seen in 1984, when cyclosporin A (CsA) was introduced (Table 3.1). This effect levelled off in later years.

Table 3.1
Graft survival (first graft, cadaveric donor) in three consecutive periods, USA 1977–88

	Development	1-year graft survival
1977-79	Azathioprine + steroids	55%
1980-83	HLA-DR matching	64%
1984-88	Cyclosporin	77%

Although combining the data from different countries and even from different centres is always a little tricky, we will nevertheless attempt this: the Eurotransplant Registry contains the graft survival results from a large number of transplant patients from 50 centres in five countries (Austria, FRG, Belgium, The Netherlands and Luxembourg), see Table 3.2.

Table 3.2
Graft survival (first grafts, cadaveric donor) in 9348 patients from Eurotransplant centres (1982–8)

	1 year	2 years	3 years	4 years	5 years
Non CsA	70%	65	59	56	53
CsA	85%	80	75	67	64

CsA, cyclosporin A. (Source: Terasaki, Clinical Transplants 1988)[38]

The results in Table 3.2 compare favourably with USA data from the same period.

In a large number of transplanted patients the beneficial effect of HLA matching is visible, even in recent years with the improved immunosuppression through the use of CsA. In the CsA-treated group, the well-matched patients (with six shared antigens) had a 5-year graft survival of 75 per cent, whereas in the worst-matched patients (no shared antigens) survival was 43 per cent. In the non-CsA treated group, this effect was even more marked, with a 5-year survival in the well-matched patients of 68 per cent, but only 17 per cent in the worst-matched patients. The conclusion can only be that beneficial matching is still worthwhile, even with improved immunosuppression.

4 THE DEVELOPMENT OF HEART TRANSPLANTATION

The history of heart transplantation is characterised by sudden leaps, dramatic successes and even more dramatic failures rather than by a slow and methodical gathering and testing of knowledge and skills. It has attracted more publicity than any other transplantation procedure. Writers who have studied the history of heart transplantation differ radically in their views: thus Moore, in his 1972 history of organ transplantation[21], writes 'unlike transplantation of other organs, progressing cautiously after a slow laboratory launch, cardiac transplantation leapt into action suddenly, quickly getting off the ground, and basing its meteoric rise on remarkably brief laboratory studies' while others, including Shumway and Stinson[39], Baumgartner[40], Griepp and Ergin[41] believe that clinical heart transplantation was the result of decades of laboratory investigation, dating back to the early part of this century and leading naturally to the first human transplant in 1967.

EARLY HISTORY

The first scientific reports of cardiac transplantations come from Carrel and Guthrie in 1905.[2] They removed hearts from puppies and sutured them into the necks of adult dogs where some of the organs functioned for several hours. However, their work was mainly concerned with developing surgical anastomosis and the transplantation of blood vessels and they were not considering any clinical application in humans at that time. Although Carrel was awarded the Nobel Prize for this experimental work, leading surgeons failed to see a future use for his findings. It was not till 1933 that Mann and co-workers at the Mayo Clinic transplanted puppy hearts heterotopically, achieving survival of up to eight years.[42] They observed that some of their failures could be attributed to some sort of biological process, now recognised as immunological rejection.

In 1950 Demikhov[43] and Sinitsin[44] again investigated cardiac transplantation in dogs. In their experiments the donor heart was placed heterotopically in the thorax in parallel with the recipient's heart in the blood circulation. Blood was routed from the right inferior pulmonary vein into the transplanted organ, which pumped the blood again into the aorta. The recipient's heart was excluded from the circulation and the entire circulatory load was transferred to the donor heart, in one experiment for 32 days. These important findings went largely unnoticed because of the isolation of the Russian scientists during the Cold War, but there is evidence that Demikhov's use of the graft in a heterotopic, auxiliary position was later adopted for clinical use by Barnard in South Africa.

In the USA and Europe interest in cardiac transplantation was revived as a result of the promising results of kidney transplantation in 1950. In 1952 Marcus (Chicago) experimented with heterotopic grafted hearts in dogs, but the best result was a disappointing 48-hour survival.[45,46] This led him to remark that the replacement of a heart in man must be considered at present a fantastic dream.

More promising was the work of Downie (Canada) who did a series of 30

heart transplants in dogs, of which 23 had good survival and function.[47] Surgically, then, cardiac transplantation was no longer an obstacle. In the late 1950s Webb[48,49] and Goldberg[50] demonstrated that orthotopic grafting of hearts was technically feasible, overcoming the problem that during the operation there is no pump to maintain circulation by using the extracorporeal circulation pump that had been developed for cardiac by-pass surgery in 1953. Kondo, in 1965, performed orthotopic heart transplants in dogs by cooling the recipient's body down to 16°C, thus slowing the metabolic process so that the body can go without circulation for one to two hours. This technique has also been used in human heart transplants, but only sporadically.

Experimental work in heart transplantation entered a new phase when in 1958 Lower and Shumway started their collaboration in Stanford and made real progress. By combining extracorporeal circulation during surgery with preservation of the donor heart in a cold saline solution and a new surgical technique (mid-atrial anastomosis), they demonstrated that the orthotopic procedure was perfectly feasible and good survival and function could be expected. The surgical part of the procedure had thus matured.[51] But graft rejection, which had already been observed by Mann in the early 1930s, was to prove the major obstacle in all organ transplantation: immunosuppression was aptly called 'the Achilles heel of organ transplantation'[52]. It was almost ten years before there was any progress in the search for effective immunosuppressive techniques and agents.

Total body irradiation and lymph node irradiation were used in the early 1960s in kidney transplantation; 6-mercaptopurine (1950) and its derivative azathioprine (Immuran) appeared in 1961, corticosteroids (prednisone) in 1962, anti-thymocyte globulin in 1966 and finally cyclosporin in 1978. In 1962 Lower *et al* made important progress: they found that incipient rejection in grafted canine hearts could be detected on the electrocardiogram in the form of changed electrical patterns.[53] Thus an effective and non-invasive diagnostic test had become available to monitor rejection in transplanted patients.

With the aid of these techniques and developments, graft survival of 250 days in a transplanted dog was achieved in 1965. On the basis of the extent and thoroughness of the experimental work, it seems that by the late 1960s cardiac transplantation in humans was a logical next step and did not come out of the blue. However, before this happened two other amazing experiments took place.

In 1964 Hardy, who had been carrying out extensive experimental investigations in heart and lung transplantation, transplanted a chimpanzee's heart into a 68-year-old patient dying of end-stage hypertensive cardiac disease. The primate heart proved too small to cope with the circulation of venous blood and could be kept going only by manual cardiac massage. After an hour it decompensated and the patient died.[54,55] Hardy concluded that the experience supported the scientific feasibility of heart transplantation in man.

Later it became known that Hardy had originally intended to implant a human donor heart, but that the donor's family had refused at the last moment so that Hardy had to resort to other solutions. Since Hardy had been experimenting with chimpanzees for some time, he felt that the use of a

primate's heart was the only option left to him. Afterwards he was severely criticised for having neglected the ethical aspects of this experiment.

In 1966 Richard Lower did the reverse experiment: he placed a human heart, seconds after it had stopped pumping, in a primate and managed to get the circulation going again. However, since the heart was too big for the monkey's chest to be closed again, the experiment had to be stopped after a while. Surprisingly, Lower never published any official report of this experiment.

THE FIRST HUMAN HEART TRANSPLANT

The first human heart transplant was performed on 3 December 1967 by Christiaan Barnard at the Groote Schuur Hospital in Capetown, South Africa.[56] The recipient was 55-year-old Louis Washansky, who – after having been on the brink of death with end-stage ischaemic heart disease – survived for 18 days before he died of rejection and sepsis. The donor had been a 25-year-old woman.

To many it came as a complete surprise that a country without any prior experience and achievement in organ transplantation would 'snatch the coveted prize' as one newspaper put it. That there was indeed a competition in progress is borne out by the fact that three days later the second heart transplant took place in the United States (Brooklyn Medical Centre). In this case the heart of an anencephalic child was implanted into a three-week-old child with a congenital heart defect. The child survived only six hours.

Barnard had not performed his transplant without careful planning. In the months before, he had been working under the supervision of Richard Lower and David Hume at the Medical College in Richmond, Virginia (USA), where he had carried out some experiments with animal hearts. As he wrote later in his autobiography, his work with Hume was only one of many experiences that led him to the first heart transplant, but it had proved a decisive one.

News media all over the world headlined Barnard's achievement, but emphasised mainly the sensational aspects and failed to put things into perspective. Barnard himself sees to have been rather uncertain about this first transplant, its timing and its outcome. His autobiographical notes reveal that he considered it to be 'a disappointment and little less than a failure'.[57]

Later, Barnard was criticised by his medical colleagues for acting prematurely and having taken too many risks. Others remarked that South Africa was at the time the only country where no discussions on brain death and its legal aspects formed an obstacle to both transplants and operation on donors.

Moore later wrote that this first transplant added little to the body of science but only created a tremendous and unprecedented world-wide publicity for a medical event.[58] Barnard knew that he had committed himself to a cause that could not be stopped; on 2 January 1968 he performed a second heart transplant on Philip Blaiberg, a Capetown dentist, this time with greater success: Blaiberg lived nearly 18 months before dying of chronic rejection and the return of his coronary artery disease.

These early events sparked off a feverish activity in cardiac transplantation all over the world. In 1968 alone 103 transplants were performed, and 1969 saw another 46 transplants. By the end of 1969 64 teams in 22 different countries were engaging in cardiac transplantation. However, soon the grim reality that none of these recipients lived more than two years and almost 70 per cent were dead within four months overcame the initial euphoria. In 1970 only 15 transplants had been done and almost all centres had stopped their activities: heart transplantation had virtually come to a standstill. Only five centres continued their programme: Stanford (Shumway), Capetown (Barnard), Paris (Cabrol), Medical College, Virginia (Lower) and Columbia University, New York.

This situation has been described as the 'heart transplant moratorium', and it continued till the end of the 1970s. Figure 4.1 shows the beginning of this moratorium, together with the continuing and increasing activity in Stanford.

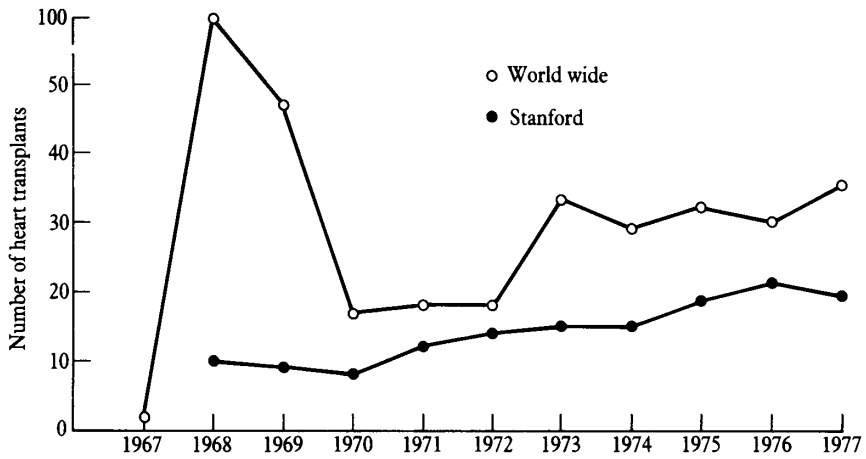


Figure 4.1.
Number of heart transplants worldwide and Stanford 1967–77

Shumway summarised his thoughts about the situation as follows:

> 'No experimental orthotopic heart graft had survived more than a few hours in South Africa when Barnard's clinical effort took the world by surprise. Suddenly heart transplants were being done in places where one would hesitate to have his atrial septum defect closed. Hardly a programme could support its clinical activity with an experimental programme, and high mortality soon had its effect on patient referral.'[59]

Figure 4.2 shows the end of the moratorium.

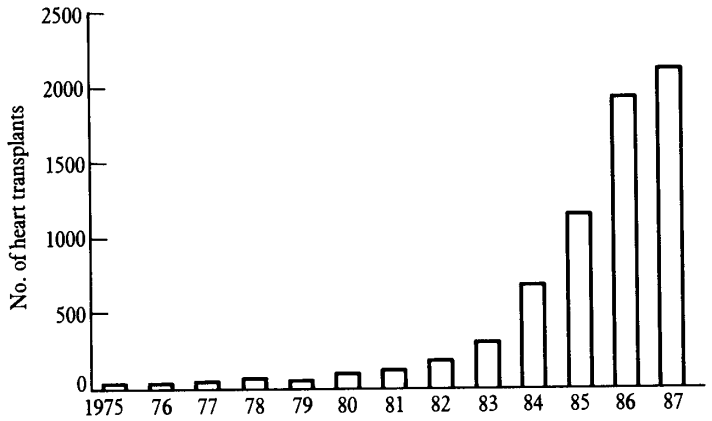


Figure 4.2
Number of heart transplants entered in the International Registry 1975–88

One cannot but agree with Shumway that most of the transplanting centres had done no prior experimental work in cardiac transplantation, whereas Stanford had a large clinical programme in kidney grafting and almost 10 years of experimental effort in heart transplantation to rely on. As a consequence Stanford was the only centre to make steady progress in heart transplantation, thanks to a strong laboratory programme. This resulted in advances in immunosuppressive drugs (rabbit anti-thymocyte globulin) and in the development of transvenous myocardial biopsy. The Stanford team also developed a carefully formulated set of indications and selection criteria for heart transplantation that was to serve later as a model for most centres. Results in heart transplantation also benefited from developments in kidney transplantation: pre-operative blood transfusions were used, which had been shown to lead to better graft survival of transplanted kidneys. Other important progress was in the field of organ preservation, to protect the explanted organ against the effects of prolonged cold ischaemia.

In spite of these advances, real improvement of patient and graft survival in heart transplantation came slowly. In 1978 Austen wrote[60] in an editorial in the New England Journal of Medicine

> 'It is now apparent that for a very few patients, under very special conditions, heart transplantation can be a rational and socially acceptable therapy, although it is obviously only a transitional and temporary answer to the problem of chronic end-stage heart disease.'

However, by 1980 things had changed and the outlook became brighter. The Stanford group published their results for 1974-1980, showing a one-year graft survival of 63 per cent and a five-year survival of 39 per cent – results that were not very different from those for kidney transplantation at the time. This and the fact that the fact that results in Stanford were steadily improving revived the interest of other centres. Most adopted the Stanford protocol when they made a new start with cardiac transplantation.

Barnard at the Capetown centre followed a course of his own after 1967. Between 1967 and 1973 he performed eleven orthotopic heart transplants. In 1974 he changed to a heterotopic grafting procedure, preferring to implant a 'tandem heart' and leaving the recipient's own diseased heart in place. This had as its main advantage that one avoided the risk of removing the patient's heart and relying solely on the new heart to start functioning. But this technique also had serious drawbacks. Although the early results were comparable to orthotopic heart transplants, the heterotopic procedure has found few followers and is seldom performed today: only 47 heterotopic transplants were performed in 1986 and 24 in 1987.

DEVELOPMENTS IN THE 1980s

A number of centres in the USA as well as in Europe made a new start around 1980. This was strengthened by the introduction of cyclosporin A in that year. After Roy Calne (Cambridge, 1979) had demonstrated[61] its efficacy – and also its negative side-effects – in kidney, liver and pancreas transplantation, the drug proved equally successful in heart transplantation.[62] Rejection episodes became less frequent and less severe, especially in the first three months after transplantation, leading to better patient and graft survival. The average hospital stay became much shorter. By 1984 developments were such that Austen could write in another editorial in the New England Journal: 'cardiac transplantation has now been generally accepted as a therapeutic intervention of proved value.'[63]

In other words, heart transplantation had come of age. This was also the conclusion of a number of evaluation studies on heart transplantation carried out by independent researchers at the request of government and health care financing agencies,[64–66] which showed that cardiac transplantation was a cost-effective procedure which could add a considerable number of life-years of good quality. Health care financing agencies in several countries decided to reimburse heart transplantation as a regular service.

However, there is still room for improvement in heart transplantation. Progress is still being made in the field of immunosuppression: so-called triple therapy (a combination of cyclosporin A, azathioprine and steroids) has improved the management of rejection, giving fewer side effects. Other new immunosuppressive drugs such as OKT-3 and FK506 are under evaluation in clinical trials, and the effect of pre-transplant matched blood transfusions is under investigation. Promising also are the new methods for organ preservation (UW and HTK fluids) that may reduce primary non-function and give longer times for testing, matching and transport.

THE RESULTS OF HEART TRANSPLANTATION

The improvement of results in heart transplantation is best demonstrated by showing the survival data for different periods. Data on large series of transplants are available for a number of individual centres (Stanford, Papworth/Harefield, Paris, Hannover); also, since 1980 the International Society for Heart Transplantation has set up a voluntary international registry to record data on heart and heart–lung transplants. Over 225 centres contribute to the registry, supplying data on approximately 2500 transplants a year. As of September 1989, the registry has gathered data on some 8200 heart transplant recipients.

Table 4.1
Graft survival for heart transplants, 1974–87

Period and sources	1-year	3-year	5-year
1974–1981 (Stanford)	63%	51%	39%
1981–1984 (Intl Registry)	70%	66%	63%
1984–1987 (Intl Registry)	85%	82%	82%

The progress in rejection control is responsible for the fact that long-term survival is almost as good as one-year survival. Individual centres now report one-year survival of up to 94 per cent in selected patients (Congress of The European Society for Organ Transplantation, Barcelona 1989). Operative mortality (first 30 days) in heart transplantation has declined from 18 per cent in 1967–77 to 9 per cent in 1988–90 at Stanford.

5 THE DEVELOPMENT OF LIVER TRANSPLANTATION

The evolution of liver transplantation started much later than kidney and heart transplantation. For no apparent reason its development has been less well documented than other forms of organ replacement. In one approach, the host liver is removed and replaced with a homograft: this is called orthotopic transplantation. Alternatively, an extra liver is implanted at an ectopic site: this is called auxiliary transplantation. Although auxiliary transplantation was important in the early experimental history of liver transplantation, it has seldom been attempted in humans. Today it is routinely performed in only one or two centres in the world, mostly in patients with acute fulminant liver failure or with too high a risk for an orthotopic procedure. Recently there has been a renewed interest in this technique, after an encouraging report from the centre in Rotterdam (Netherlands).[67] In this review we will only be concerned with orthotopic liver transplantation.

EARLY HISTORY

The first known attempts at experimental orthotopic transplantation of the liver were made by Jack Cannon of Los Angeles whose animal experiments were briefly described in the Transplantation Bulletin in 1956.[68] Cannon failed to obtain any liver function after implantation and his animals quickly died.

In June 1958 an experimental programme in orthotopic transplantation of the canine liver was started at the Peter Bent Brigham Hospital – already famous for its early successes in clinical kidney transplantation – under the direction of Frances D Moore. Soon after this Thomas Starzl started similar experiments at North Western University in Chicago. In these first experiments the emphasis was on understanding the technical problems and no significant survival resulted. In the first reports that appeared in 1961 in the Journal of Surgery in Gynaecology and Obstetrics (!) Starzl described the features of rejection observed in these dogs, which were not treated with any kind of immunosuppressive therapy.[69]

Around 1965, with the use of azathioprine and anti-lymphocyte globulin long-term survival was achieved in mongrel dogs, one transplanted dog living for almost twelve years. In the same year Garnier in Paris reported improved survival after liver transplantation in pigs.[70] It appeared that the rejection phenomenon in pig homografts was mild in comparison to that in dogs, even without the use of immunosuppression. This observation was confirmed by groups in Bristol (Peacock), Cambridge (Calne) and Denver (Starzl). These experiments have contributed greatly to the understanding of different aspects of liver transplantation.

CLINICAL LIVER TRANSPLANTATION

In the wake of these experiments the first attempts at liver transplantation in humans were made by Starzl in the early 1960s. However, these were xeno transplants in which baboon livers were implanted in terminally ill patients, all of whom died almost immediately after the operation.

On 1 March 1963 Starzl made the first attempt to replace a human liver with a homograft at the University of Colorado (Denver, USA). This and four other attempts over the next seven months were all unsuccessful. Nevertheless other centres followed Starzl's example and attempted clinical transplantation: Moore (September 1963, Boston) and Demirleau (January 1964, Paris). All these attempts failed and in the next years these clinical trials came to an almost complete stop. Finally on 23 July 1967 Starzl succeeded in getting extended survival after transplanting a liver in a 1½-year-old girl with hepatocellular carcinoma.[71] She survived for 13 months before dying from metastases of the original carcinoma. This first successful liver transplantation took place in the same year as the first heart and pancreas transplants.

On 2 May 1968 Calne and Williams (University Hospital, Cambridge and King's College, London) treated the first patient in a programme that was to become one of the largest in the world.[72]Calne had already been successful in kidney transplantation and had contributed significantly to the development of chemical immunosuppression. In that same year liver transplantation programmes also started in France (Paris) and Germany (Hannover).

Starzl had taken the lead by using a new immunosuppressive regimen, a combination of azathioprine and prednisone. In this way he built up a series of 230 transplants between 1967 and 1982, working at Denver and later in Pittsburgh. By that time cyclosporin had become available and was evaluated in clinical liver transplantation by Calne, who reported progress on the first 125 patients up to 1982.[72]

Despite the early start the results of liver transplantation were in general less good than for other types of organ transplantation, and improvement came more slowly. Before 1980 there were only four major centres in the world doing liver transplants on a regular basis: Pittsburgh, Cambridge, Hannover and Groningen (Netherlands). Single attempts and small series in the years between 1969 and 1978 have been reported from a number of centres such as: Boston, Paris, Los Angeles, Bonn, Sao Paulo, Minnesota, Manchester and Oslo.

In the first 20 years after its introduction, liver transplantation has been performed in Europe at a much slower rate than in the USA. In 1980 only seven centres were transplanting livers in Europe, while in the States 22 centres were already active or had tried the procedure at least once. Part of this difference in diffusion is explained by the fact opinions differed concerning the stage of the disease at which the patient should be operated on. The US centres used a less strict set of criteria than their European counterparts. Also repeat transplantations were rarely done in Europe at that time, while in the States they were performed more readily and at a much earlier stage. Many of the patients who were transplanted in the States were not considered eligible for liver transplantation in Europe at that stage of development. *Figure 5.1* shows the difference in diffusion rate between Europe and the USA between 1963 and 1985.

By 1983 the picture had changed: in June of that year the National Institutes of Health held a Consensus Conference in Washington to discuss the status of liver transplantation. Evidence was presented showing improvements in surgical techniques and post-operative care, donor organ selection and

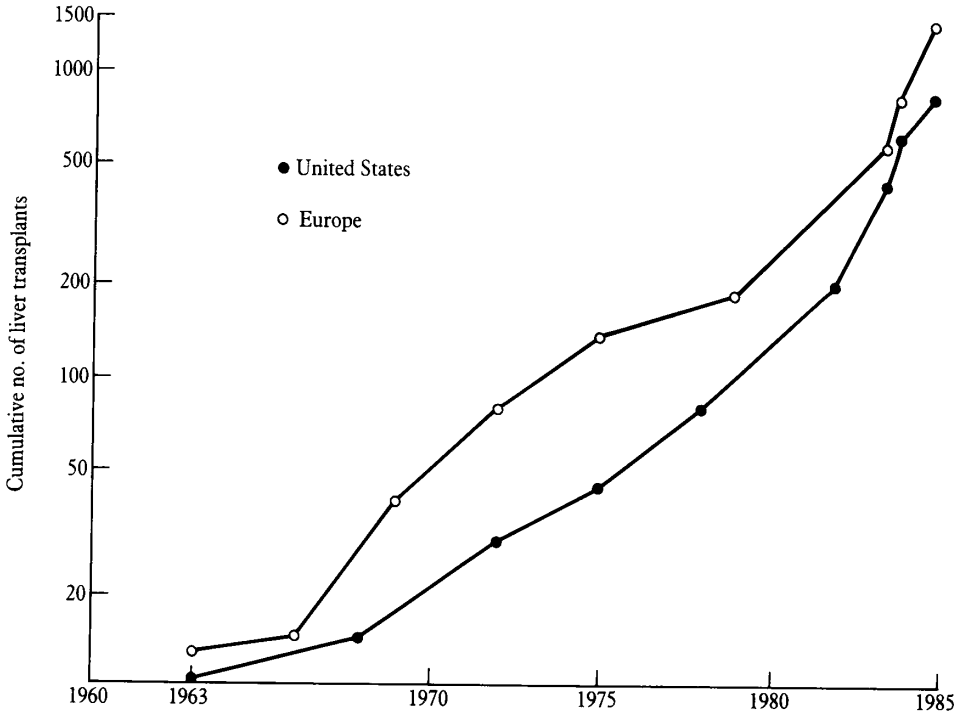


Figure 5.1
Cumulative number of liver transplants in Europe and USA, 1963–85

preservation, immunosuppression, selection of patients and timing of surgery. The one-year survival rate was at that time approaching 40–45 per cent in the leading centres. Even with a mortality rate of 40 per cent in the first month after surgery, the conference concluded that liver transplantation was a therapeutic modality for end-stage liver disease that deserved broader application.

Since this Consensus Conference, activity in liver transplantation on both sides of the Atlantic has greatly increased. By 1985 no fewer than 34 centres were active in Europe, doing a total of 225 transplants in that year alone. In the USA 42 centres performed 602 liver transplants in 1985, Starzl in Pittsburgh had done a total of 668 by the end of 1985 and 272 during that year.

During recent years liver transplantation has continued to expand due to a broadening of indications, diminished contra-indications and increasing referrals to transplant centres. The US Liver Transplant Registry (begun in September 1987) collects data from all US centres (42 in 1988); the number of transplants is now levelling off at around 1600 per year. In Europe the European Liver Transplant Registry (Bismuth, France) reported 2414 transplants performed by 49 centres as of April 1988.

Because of the shortage of liver donors, new surgical procedures have been developed to meet the demand: adult donor livers are now being reduced in size for paediatric recipients, and livers are being segmented to be implanted into two recipients. Recently, a team in Chicago (Broelsch) has started performing liver transplants in young children with congenital liver disease, using part of their parents' livers (live donor).

RESULTS OF LIVER TRANSPLANTATION

It is difficult to make a comparison of results of liver transplantation in different time periods and between different centres. This is because indications, case mix and methods of immunosuppression differ widely. The development over time in the oldest and largest centre (Starzl, Denver and Pittsburgh), however, shows[73] the development in one-year survival in selected patients from 25 per cent in 1967–73 to 76 per cent in 1984–7, cyclosporin A having been introduced in 1980.

However, if one looks at the average one-year survival in *all* patients, the improvement over time has been less good, the European Registry showing one-year survival of only 44 per cent in 1984–87 compared with 60 per cent for Pittsburgh and 69 per cent for Cambridge. Today, the overall one-year survival rates in the larger centres are 60–85 per cent, depending on case mix. Five-year results may vary from 65 to 88 per cent (*Table 5.1*).

Thus, the best prognosis is for patients with primary biliary cirrhosis (PBC), in some patients with acute fulminant hepatic failure and for children with congenital biliary atresia. Prognosis is less good for patients with post-hepatic cirrhosis and with malignancies of the liver (hepatocellular carcinoma).

Table 5.1
One- and five-year survival for different indications with liver transplantation (1988)

Diagnosis	1-year	5-year
Primary biliary cirrhosis	69%	65%
Other cirrhoses	56%	50%
Sclerosing cholangitis	77%	77%
Fulminant hepatic failure	78%	78%
Malignancy (HCC)	71%	35%
Biliary atresia (paediatric)	90%	88%

Sources: UCLA Registry, Calne, Slooff, Pichlmayr

6 THE DIFFUSION OF ORGAN TRANSPLANTATION IN EUROPE

All countries that have started kidney transplantation, and especially the grafting of cadaveric kidneys, have developed facilities for tissue typing and matching, organ procurement and organ exchange. In most European countries this has not been at the instigation of governments or health care delivery agencies: most of these services have sprung from private or semi-public organisations such as associations of dialysis patients, kidney foundations or even transplant centres themselves. The role of governmental and public health agencies has been remarkably 'low key'. They have usually been involved only when problems arose in the field of insurance and reimbursement, cost containment, planning of transplant facilities or legislation concerning organ donation and procurement. Most governments also have done little to promote organ donation and transplantation.

We therefore start by examining kidney transplantation and the general infrastructure created for organ procurement and transplantation, and consider heart and liver transplantation as more or less natural developments of kidney transplant programmes.

Data for this study come from a wide variety of sources: comparative data from international registries such as the European Dialysis and Transplant Association (EDTA – now called European Renal Association), the International Heart Transplant Registry and the European Liver Transplant Registry; data for individual countries from the annual reports of national or supra-national organ procurement and exchange agencies such as Scandia Transplant, Eurotransplant, UK Transplant Service, and France-Transplant; and for the USA, reports from the United Network for Organ Sharing (UNOS) and the Department of Public Health as well as material from the Congressional General Accounting Office (GAO). Whenever possible, data and figures have been checked from more than one source. We found many inconsistencies and significant differences in the data, especially in those from the international registries, in which case we have tried to check this against material from individual transplant centres in the countries concerned.

To facilitate comparisons between the countries studied, we give not only absolute numbers but also numbers of transplants or centres 'per million population' (pmp). Whenever relevant, we have compared developments in Europe with those in the USA.

COUNTRIES INCLUDED IN THE STUDY: GENERAL DATA

The EC countries are presented as a group whenever this is relevant. However, since some of the non-EC countries (eg Sweden, Norway) have played an important role in the diffusion of organ transplantation in Europe, and also co-operate with the EC countries in supra-national organ exchange networks (eg Austria), we have included these countries. Turkey too is included because, although it has only recently started organ transplantation, there is substantial co-operation with other European countries and supra-national agencies. Eastern Europe has been omitted, because of the extreme difficulty of obtaining reliable and recent data.

Table 6.1 shows the population of all countries entered in this study, for 1980 and 1987.

Table 6.1
Population of European countries and USA (1980/87)

Country	Population (x1000) 1980	1987
Denmark	5.1	5.1
W. Germany	61.6	60.8
Netherlands	14.2	14.6
Belgium	9.8	9.8
Luxembourg	0.4	0.4
France	53.7	55.6
United Kingdom	55.6	56.8
Ireland	3.4	3.6
Spain	37.4	38.8
Portugal	9.7	10.2
Italy	56.1	57.3
Greece	9.6	10.0
Total Europe I (EC)	316.6	323.0
Sweden	8.2	8.3
Norway	4.1	4.2
Finland	4.7	4.9
Switzerland	6.3	6.5
Austria	7.5	7.5
Turkey	44.4	52.8
Total Europe II (non-EC)	75.2	84.2
Total Europe I + II	391.8	407.2
USA	227.6	230.8

Sources: OECD 1987; Hospital Committee of the EC 1990

Population growth is concentrated in the south of Europe and Turkey. We have not examined the age, sex and health profiles of these populations, although this may have some relevance for organ transplantation.

Table 6.2 shows health care expenditure in the 18 European countries, which ranges from 4.5 per cent to 9.5 per cent of the gross national product (GNP). Greece, Spain, Portugal and the United Kingdom are at the low end of the scale: 4.5–6 per cent. The Scandinavian countries (other than Sweden) and Belgium are in an intermediate position with an average of 6.5 per cent, while the rest of Europe approaches 8–9 per cent. The leader in Europe is Sweden with 9.4 per cent; however, the USA exceeds the others by far at 11.5 per cent of GNP.

Table 6.2
Health economy data, Europe and USA. Health care expenditure in % GNP and per capita (US$) in 1980 and 1987

	1980		1987	
Country	%GNP	US$ per capita	%GNP	US$ per capita
Denmark	6.8	879	6.3	800
W. Germany	7.9	1065	8.1	1031
Netherlands	8.2	983	8.6	984
Belgium	6.1	747	6.2	826
Luxembourg	6.7	845	6.4	968
France	8.5	1036	9.1	1039
United Kingdom	5.6	530	5.9	711
Ireland	8.5	480	8.0	549
Spain	5.9	334	5.8	486
Portugal	5.9	151	5.5	310
Italy	6.8	479	7.2	764
Greece	4.2	175	4.6	245
Sweden	9.7	1010	9.4	1195
Norway	6.8	963	6.3	1021
Finland	6.3	677	6.6	900
Switzerland	7.2	1050	7.8	1217
Austria	7.0	718	7.2	903
Turkey	?	?	?	140
USA	9.5	1087	11.5	1926

Sources: OECD 1987; Health Data Bank

More insight is gained by looking at the health expenditure per country expressed as per capita expenditure. Now Switzerland tops the bill with US$1217 in 1987, with most north-western European countries following at US$800 – US$1200. In these countries expenditure has remained constant at this level for some years. In contrast, expenditure in most of southern Europe, the UK and Ireland is considerably less, though steadily growing over the years. As expected, expenditure per capita in the USA is much higher, being almost double that of the richest countries in Europe.

THE DEVELOPMENT OF ORGAN TRANSPLANTATION IN EUROPE

Table 6.3 gives some dates which can be considered milestones in the European development of organ transplantation.

Table 6.3
Organ transplantation in Europe: some milestones in its development

1955	First successful transplantation of a kidney from a living donor (Paris)
1960–66	Unraveling of the HLA system as basis for tissue-typing and matching (Dausset, van Rood)
1962	First successful transplantation of a kidney from a deceased donor (Edinburgh)
1967	Start of Eurotransplant: first organ-exchange agency in Europe (Netherlands)
1968	First European liver transplantations (Paris and Cambridge)
1968–9	First European heart transplantations (Paris, London, Munich and Zurich)
1970	Moratorium on heart transplantation (except for Paris)
1972	Discovery of immunosuppressive properties of cyclosporin (Borel)
1978	First use of cyclosporin A in kidney transplantation (Calne – Cambridge)
1979–81	Heart transplantation resumed in Europe following success in Stanford (UK – Harefield/Papworth, Munich)
1983	Rapid growth of liver transplantation programmes following NIH Consensus Conference (Washington)

Kidney transplantation started in Europe at almost the same time as in the USA. There had for years been intense rivalry between the USA and Europe (especially France and the UK), which began with the experimental work of Carrel and Guthrie, and in the early 1950s culminated in the first clinical kidney transplants being performed by the groups in Boston and Paris.

Western Europe then took an important lead in the development of transplant biology and immunology, 'discovering' the intricacies of the HLA system and laying the foundation for tissue typing and matching, which made possible the widespread use of cadaveric donor kidneys, allowing them to be exchanged between centres and countries. The first supra-national exchange organisation which sprang from this was Eurotransplant, based in The Netherlands and providing services for FRG, Austria and the Benelux countries. It was the first agency of its kind in the world, and has served as a model for many similar national or international organisations (including UNOS in the USA, created in 1986).

Although experimental work on heart and liver transplantation had been carried out simultaneously on both sides of the Atlantic, clinical transplantation in Europe took longer to develop than in the USA. Heart transplantation was started both in the USA and in Europe in 1967/68 as a reaction to Barnard's first attempt in South Africa; however, by 1970 all activity in Europe (except in Paris) came to a standstill. This voluntary 'moratorium' lasted in Europe till 1979, when heart transplantation was resumed in the UK. In the same period heart transplantation in the USA was kept going – and made important progress – at the Stanford centre and at the Medical College in Richmond, Virginia. The introduction of cyclosporin in the Stanford programme in 1980

Kidney transplantation in individual European countries

Kidney transplantation started in different European countries over a lengthy period: between 1954 and 1980 (Figure 6.2).

Figure 6.2
Start of kidney transplant programmes in Europe

Starting period	Countries	
Pioneers	United Kingdom	
1954–60	Norway	
	Italy	
	France	
Early adopters	W. Germany	Sweden
1961–66	Belgium	Denmark
	Finland	Ireland
	Austria	Switzerland
	Spain	Netherlands
Late adopters	Greece	
1967–80	Portugal	
	Turkey	
	Luxembourg	

Among the countries that started kidney grafting early (here called 'pioneers'), the UK and France were particularly active in both the scientific and the clinical developments. The rather late start of Greece, Portugal and Turkey has much to do with the lack of a suitable infrastructure for organ procurement and with logistical problems in their health care systems. Luxembourg on the other hand has an effective health care system, but has relied for a long time on transplant facilities in Belgium – and still does so for transplants other than of kidneys.

Table 6.5 shows the growth of kidney transplantation in each of the European countries between 1975 and 1988, in absolute numbers of transplants as well as the number pmp. The cumulated number of transplants over this period is also given.

This list shows the rather large variation between countries. All Scandinavian countries had a sizeable transplant programme as long ago as 1975 and have continued to grow ever since, Sweden and Norway reaching 40 transplants pmp in 1988. The somewhat disappointing development in Denmark is caused by a sharp fall in the number of donors in the last few years as the result of a lengthy public debate on the 'brain death' criterion.

Very substantial (10-fold) growth has taken place in FRG, Spain, France and Austria. Southern European countries have had a later and slower start than in the north and the west of Europe. Some of these countries are still in the first stages of development.

Table 6.5
Development of kidney transplant programmes in individual European countries (1975–88). All kidney transplants (CAD and LRD)

Country	1975		1988		cumulative
	abs.	pmp	abs.	pmp	1975–88
Denmark	130	25.4	146	28.6	2168
W. Germany	201	3.3	1736	28.5	12422
Netherlands	193	13.5	418	28.6	4391
Belgium	146	14.8	375	38.3	3176
Luxembourg	–	–	6	15.0	27
France	340	6.3	1808	32.5	12420
United Kingdom	731	13.1	1790	31.5	16748
Ireland	25	7.3	78	21.6	756
Spain	25	0.6	1018	26.2	7164
Portugal	2	0.2	202	19.8	769
Italy	139	2.4	658	11.5	4153
Greece	14	1.4	91	9.1	484
Total Europe I (EC)	1946	6.1	8326	25.7	64678
Sweden	192	23.4	355	42.7	3792
Norway	112	27.3	170	40.4	1792
Finland	91	19.3	156	31.8	1712
Switzerland	123	19.5	208	32.0	2424
Austria	94	12.5	307	40.9	2853
Turkey	–	–	280	5.3	977
Total Europe II (non-EC)	612	8.2	1475	17.5	136550
Total Europe I + II	2558	6.5	9801	24.1	78228
USA	3750	16.6	9150	39.7	82017

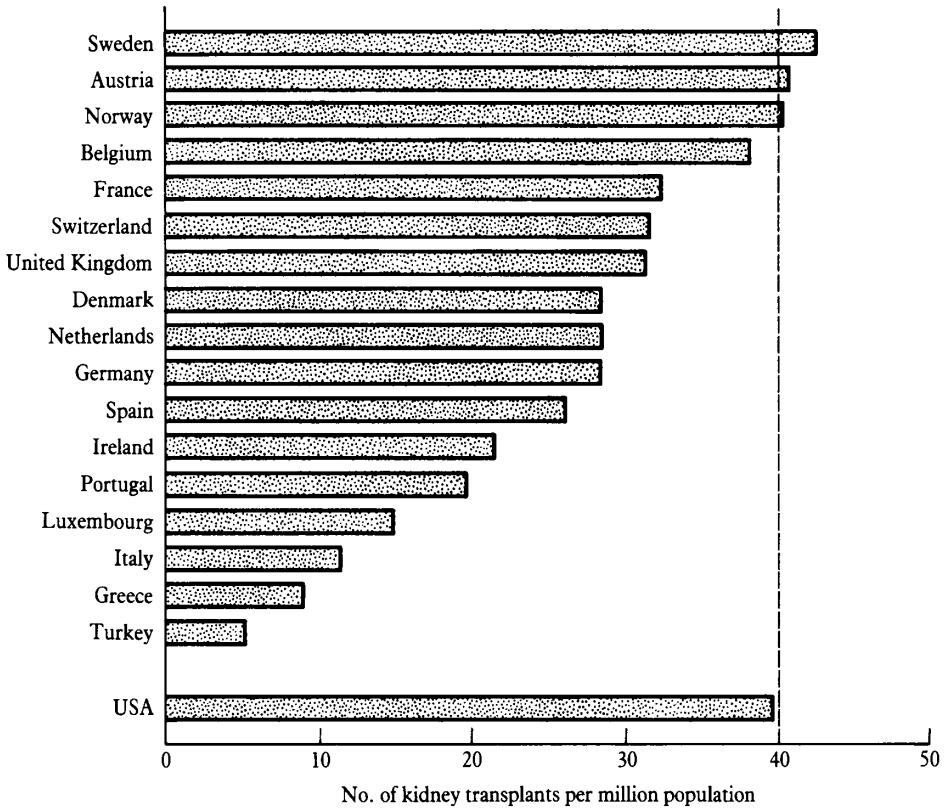
The position of Italy is extraordinary: this country started kidney transplantation as long ago as 1957, but has failed to develop its programme as most of the 'pioneers' in western Europe did. This is caused mainly by organisational and financial problems in the whole of the health care system. There is however a significant difference in development between northern Italy and the South and Central regions, which lag far behind.

In comparison with the USA, Europe still has a long way to go, although a number of European countries (Sweden, Norway, Austria and Belgium) have reached the same level as the USA.

In Figure 6.3 the European countries are ranked according to the number of transplants pmp in 1988. By 1988, only three European countries reached the annual 'target' for the 1980s (set in policy documents of many national organ procurement agencies) of 40 kidney transplants pmp. Again, countries in the

south of Europe are in the bottom half of the list. The reason for this is partly to be found in the donor procurement activities in each of the countries, which we examine in the next paragraph.

Figure 6.3
Kidney transplantation rate in European countries in 1988
(CAD + LRD transplants)
(ranking according to number of transplants per million population)

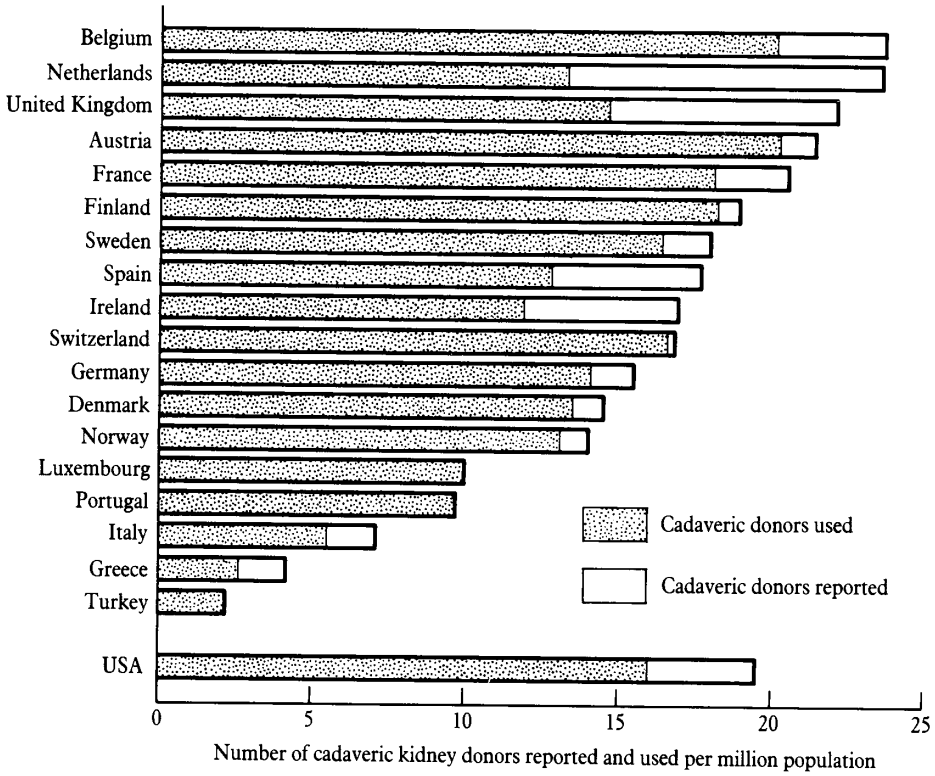


The effectiveness of donor procurement in Europe

The success of kidney transplant programmes is largely dependent on the effectiveness of the donor procurement activities in a country, and the institutions and arrangements made for this purpose. Figure 6.4 shows the donor procurement rate in each of the European countries in 1988, ranked from the highest to the lowest.

Figure 6.4 shows the number of potential donors (donors identified and recorded) as well as the number of actual donors (donors recorded and used) per million population. The difference between the two is the so-called 'discard rate', and is due to a number of reasons, including refusal of consent on the part of the family; medical unsuitability; no suitable recipient available; no transport available; no surgical or intensive care facilities available.

Figure 6.4
Effectiveness of donor procurement in Europe and USA in 1988



A high discard rate can be noted in The Netherlands, the UK, Spain and Ireland, countries that have a favourable number of potential donors. Discard rates are generally very low in the Scandinavian countries and in Switzerland. In general the effectiveness of donor procurement is much higher in the north and west of Europe than in the south. However, the data on the discard rate in countries in Southern Europe are not reliable, and the picture may be somewhat distorted.

The use of cadaveric donors and living related donors

Figure 6.1 showed that kidney transplantation in the USA relies to a considerably greater extent on living related donors than in Europe taken as a whole. In both regions the proportion of living donors in the total number of transplants is gradually decreasing, reflecting the improvement in immunosuppressive treatment and the effectiveness of HLA matching for cadaveric donors. However, the situation in the different European countries is not uniform. Table 6.6 shows the striking variation in the way living donors are employed in these countries.

Table 6.6
CAD and LRD transplants in European countries (1988)

Country	all transplants pmp	CAD transplants pmp	LRD transplants pmp	LRD as % of all transplants
Sweden	42.7	32.2	10.5	25%
Austria	40.9	36.3	4.6	11
Norway	40.4	25.0	15.4	38
Belgium	38.3	34.9	3.4	9
France	32.5	31.3	1.2	4
Switzerland	32.1	30.0	2.1	7
Finland	31.8	28.5	3.3	10
United Kingdom	31.5	29.1	2.4	8
Denmark	28.6	24.7	3.9	14
Netherlands	28.6	26.1	2.5	9
W. Germany	28.5	27.9	0.6	2
Spain	26.2	25.4	0.7	3
Ireland	21.6	21.1	0.5	3
Portugal	19.8	19.3	0.5	3
Luxembourg	15.0	12.5	2.5	17
Italy	11.5	10.4	1.1	10
Greece	9.1	2.6	6.5	72
Turkey	5.3	1.0	4.3	80
USA	39.7	31.7	8.0	20%

All Scandinavian countries have a proportion of over 10 per cent living related donors (LRD), with Norway in the lead with 38 per cent in 1988. The high overall rate of kidney transplants pmp in these countries is partly explained by this phenomenon. One may justly conclude that the use of living donors is socially and culturally accepted, and medically promoted, in Scandinavian society.

In striking contrast is a group of European countries with a very low proportion of LRDs, among them France, FRG, Spain, Portugal and Ireland. Since most of these countries have a transplant programme that has been running for 20 years, one may conclude that the use of living donors in these countries is discouraged for social and/or medical reasons.

On the other hand the very high proportion of living donors in Greece and Turkey reflects the stage of development of the transplantation programme rather than medical attitudes: procurement of cadaveric donors (CAD) has only just started in these countries.

The USA is similar to the Scandinavian countries as far as the use of LRDs is concerned: a proportion of 20 per cent or more living donors reflects a positive attitude among the public and the medical profession in this respect.

The relationship between dialysis and kidney transplants

The close relationship between dialysis and kidney transplantation is illustrated in Table 6.7, which shows the number of people on dialysis and with a functioning kidney graft in the different countries in 1988.

Table 6.7
Number of patients alive on renal replacement therapy (RRT) in Europe in 1988

	all patients alive on RRT		patients alive on dialysis		patients with functioning graft	
Country	abs	pmp	abs	pmp	abs	pmp
Belgium	4406	448	2861	291	1545	157
W. Germany	26747	439	20937	344	5810	95
Switzerland	2807	431	1578	242	1229	189
Luxembourg	168	419	129	322	39	97
Austria	3114	414	1901	253	1213	161
Sweden	3299	396	1399	168	1900	228
Netherlands	5462	373	2953	202	2509	171
France	20019	359	15401	276	4618	83
Spain	13638	351	9395	242	4243	109
Italy	18929	329	15445	269	3484	60
Denmark	1658	325	813	159	845	165
Portugal	3223	315	2663	261	560	54
Norway	1256	305	204	49	1052	256
Finland	1457	296	518	105	939	191
United Kingdom	16155	283	7751	136	8404	147
Ireland	811	224	315	87	496	137
Greece	2031	202	1835	183	196	19
Turkey	2380	44	1441	27	938	17

Source: EDTA 1990

Countries are ranked according to the proportion of their patient population alive on renal replacement therapy (RRT) in 1988. In the last four columns these figures are broken down into the volume of patients on dialysis (all forms of dialysis) and those with a functioning graft.

The explanation of the differences between countries is rather complicated: a high or low overall figure for the patient population on RRT may reflect epidemiological variations (incidence of renal disease) as well as medical attitudes towards the use of renal replacement therapy, for example a policy of admitting few patients to these expensive kinds of treatment.

All Scandinavian countries have a large proportion (pmp) of patients with a functioning graft. This reflects the fact that these countries have a very active transplant policy, which keeps the dialysis population relatively small and stable. Countries like Belgium, Austria, Switzerland and France, although actively promoting transplants, have not yet been able to stabilise or reduce

their population on dialysis, and therefore have a large number of patients on RRT.

A special case is FRG, which has by far the largest dialysis population, but is doing rather poorly at transplanting.

These variations are further caused by differences in dialysis policy (criteria for acceptance in a dialysis programme) and financial policies (reimbursement of RRT). The UK provides a good example; here there are financial constraints on admitting patients to dialysis and transplantation is generally favoured, but not available to many patients because of the donor shortage. The result is a relatively small population on RRT.

A further illustration of the relation between dialysis and transplantation is given in Table 6.8, which shows the proportion of dialysis patients on the transplant waiting list in 1988 in each of the countries.

All countries in the west and south of Europe have long waiting lists (60–100 patients pmp); this need for transplants cannot be met because of the shortage of donor organs. The situation is becoming worse since in most

Table 6.8
Number of patients on the transplant waiting-list and the number of transplants performed in 1988

	patients on waiting list on 31/12/88		patients transplanted in 1988	
Country	abs	pmp	abs	pmp
Denmark	225	44.1	146	28.6
W. Germany	5849	96.2	1736	28.5
Netherlands	1317	90.2	418	28.6
Belgium	803	81.9	375	38.3
Luxembourg	20	50.0	6	15.0
France	4075	73.2	1808	32.5
United Kingdom	3700	65.1	1790	31.5
Ireland	167	46.3	78	21.6
Spain	5000	128.8	1018	26.2
Portugal	1311	128.5	202	19.8
Italy	4000	69.8	658	11.5
Greece	556	55.6	91	9.1
Sweden	345	41.5	355	42.7
Norway	100	23.8	170	40.4
Finland	185	37.7	156	31.8
Switzerland	370	56.9	208	32.0
Austria	1116	148.8	307	40.9
Turkey	756	14.3	280	5.3
USA	14000	60.8	9150	39.7

Source: EDTA 1990/Council of Europe 1989.

countries there is a policy of easy acceptance to the waiting list, and criteria for kidney transplantation are broadening. Some countries (Austria, Belgium and Switzerland) are now achieving a position where the waiting list is no longer growing, because the yearly number of transplants equals the new entries on the list.

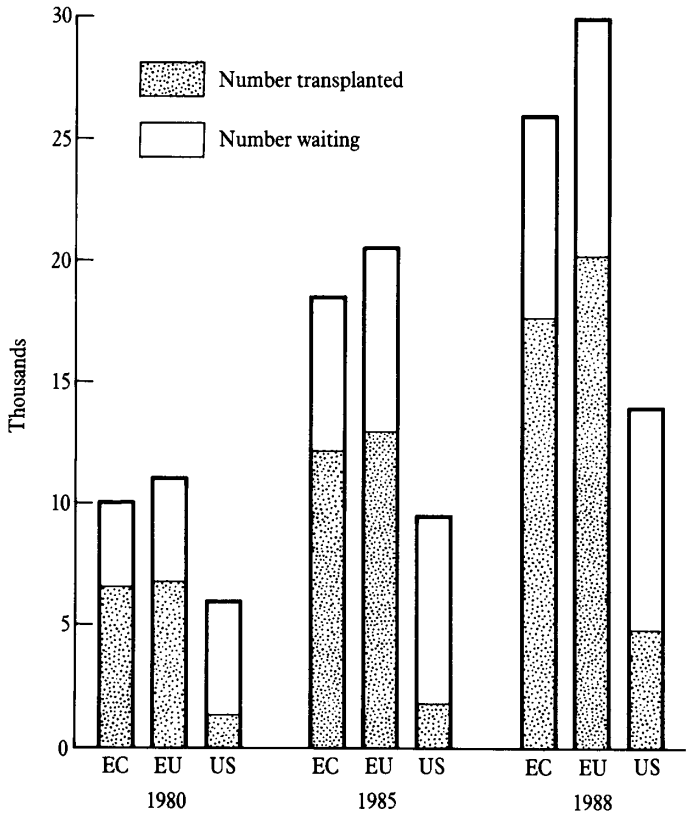
The situation in Scandinavia is very different from the rest of Europe: in all the Nordic countries (except Denmark in the last two years) the number of transplants equals the number on the waiting list. As a result the single waiting list for the whole of Scandinavia, handled by the Scandia Transplant Service, has been stable over a number of years and is now even decreasing.

The most unfavourable situation is to be found in the south of Europe (Spain, Portugal, Italy and Greece), where the growth of the waiting list outstrips the number of transplants.

The gap between waiting lists and transplants performed

The problem that in all but a few countries the waiting list cannot be matched by the annual number of transplants (often called 'the transplant gap') applies on both sides of the Atlantic. Figure 6.5 illustrates the situation in Europe and in the USA in the period 1980–8.

Figure 6.5
The gap between waiting list and transplants performed 1980–8 comparing EC, All Europe and USA



This diagram shows clearly that in all regions the gap between the number of patients waiting and the number of patients being transplanted is widening. Over the years the number of transplants in the EC and the whole of Europe is only 30 per cent of the total waiting list, even where the number of transplants in that period has doubled.

In the USA the situation has been better, with the number of transplants being roughly 70 per cent of the waiting list. In the last few years, however, this proportion is going down.

The number of transplant centres in European countries

The success of organ procurement and transplant policies in different countries is reflected, to a certain extent, in the growth of the number of transplant centres. Table 6.9 shows the development in Europe and the USA in 1980–8, and shows that Europe is catching up with the USA, although the number of transplant centres in the USA per million population is still considerably larger.

Table 6.9
Growth of the number of kidney transplant centres in Europe and USA, 1980–8

Region	1980		1985		1988	
	No. of centres	mill. pop. per centre	No. of centres	mill. pop. per centre	No. of centres	mill. pop. per centre
Europe	120	3.2	183	2.1	219	1.8
USA	150	1.5	170	1.3	190	1.2

The situation in Europe is sketched in more detail in Table 6.10, which shows the data for each country.

These data show that kidney transplantation has become an established clinical service in almost every European country, and that the size of population served by transplant centres in the different countries does not vary greatly. The exceptions are Norway, Finland and Ireland, where there is only one centre acting as the national transplant referral centre. This of course results in a relatively high 'production' per centre, when compared to the average number of transplants per centre in other countries. However, it is not possible to draw any conclusions from the average productions shown in this table, since these averages do not reflect reality. In almost all countries one finds a few large centres, doing 100 or more transplants a year, and many small centres – which may have a negative effect on the 'quality' of these transplants in terms of peri-operative complication rate and survival.

Table 6.10
Number of kidney transplant centres in Europe and USA in 1988; number of inhabitants per centre and average number of transplants per centre

Country	Centres	Pop. per centre (millions)	Average no. of transplants
Denmark	4	1.3	36
W. Germany	28	2.1	62
Netherlands	9	1.6	46
Belgium	8	1.2	47
Luxembourg	1	0.4	6
France	41	1.3	44
United Kingdom	39	1.4	46
Ireland	1	3.6	78
Spain	30	1.3	34
Portugal	8	1.3	25
Italy	24	2.4	27
Greece	2	5.0	45
Sweden	4	2.0	89
Norway	1	4.2	170
Finland	1	4.9	156
Switzerland	6	1.1	35
Austria	6	1.2	51
Turkey	6	8.8	46
USA	190	1.2	48

The future need for kidney transplantation in Europe

The current situation on the diffusion of kidney transplantation in Europe and the USA can be summarised differently, by comparing the estimated need for transplants with the number of transplants currently performed (Table 6.11).

Table 6.11
The need for kidney transplants in Europe and USA in 1990

	Situation 1988		Needed 1990	
Region	pmp	abs	pmp	abs
EC countries	25.7	8326	45	14,535
All Europe	24.0	9790	45	18,300
USA	39.7	9150	45	10,350

In this table the actual number of kidney transplants in 1988 is compared with the estimated need for kidney grafting in the year 1990, put at a minimum of 45 transplants pmp. The first conclusion is that Europe (and the EC in particular) still has a long way to go to fulfil the need. Things may look a lot brighter in the USA, but this is only a superficial impression: the dialysis population in the USA has recently been growing at a higher rate. As a result the proportion of dialysis patients on the transplant waiting list is also increasing (over 18,000 in 1990). A second development is that transplant policies are also changing: more older people and more diabetics are transplanted, and more re-transplants are performed. It is not yet possible to tell at which point this will level off, but it is reasonable to estimate the need for transplants in the coming years in the USA at 50–55 pmp. These developments call for new incentives to improve the donor procurement rates and to increase transplant programmes in the coming years, in Europe as well as the USA.

THE DIFFUSION OF HEART TRANSPLANTATION IN EUROPE

Clinical heart transplantation started in 1967 when Christiaan Barnard performed the first human heart transplant in South Africa. Within days of this event transplantations were also performed in the USA (first transplant 1967, first at Stanford 1968) and in Europe (first transplant, Paris 1968).

Development of heart transplantation in Europe and the USA, 1967–88

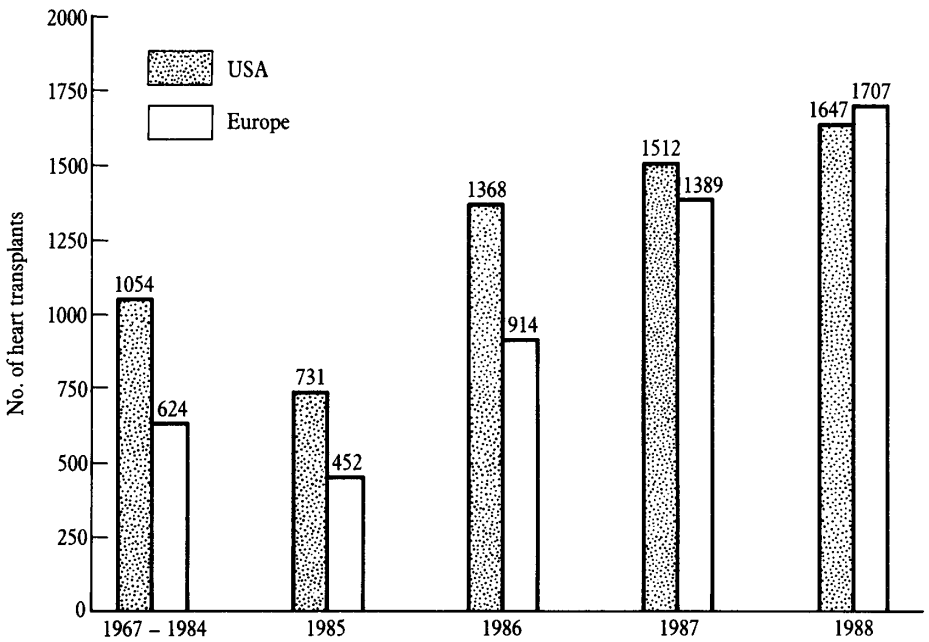
The early start of heart transplantation in 1967 (by some deemed 'premature') was followed by a period of world-wide, almost frantic activity. However, when the results turned sour, the interest in heart transplantation died down and by 1970 all but four centres (Capetown, Stanford, Richmond Virginia and Paris) had abandoned their clinical programmes. Heart transplantation entered a period of 'voluntary moratorium', which lasted until 1979. A number of centres in the USA then resumed their activity (spurred on by the success in Stanford) and the number of programmes and transplants grew considerably. In Europe, however, the new start was made with some hesitation, and for some years the UK (at Papworth and Harefield) remained the only country in Europe, apart from France which had continued its early activity, to perform heart transplants. This slow re-start of heart transplantation in Europe is illustrated in Figure 6.6, which shows transplant activity before and after 1985.

Figure 6.6 illustrates the lead that the USA had taken over Europe in the period 1967–84, during which the USA almost doubled its number of transplants while developments in Europe were very modest. After 1984 Europe made good this slow start and caught up with the USA, reaching the same number of cardiac transplants in 1988. However, if we look at the number of transplants per million population, the picture that emerges is

quite different. In 1988 the USA was far ahead with 7.2 transplants pmp, against 4.2 pmp in Europe. This means that the over-all level of activity in heart transplantation in the USA is still considerably higher than in Europe.

In recent years things have been changing, with the growth of heart transplantation in the USA slowing down as the result of the shortage of donors, while in Europe the over-all activity is speeding up as more countries develop regular heart transplant programmes. We may expect the number of heart transplants in Europe to continue growing in the coming years. This will be possible even if the total number of donors remains constant, since the proportion of multi-organ donors has not reached its maximum in most countries.

Figure 6.6
Development of heart transplantation in Europe and USA, 1967–88



Cumulative number of heart transplants, 1967 – 1988: USA 6312, Europe 5094

The start of heart transplant programmes in Europe

Figure 6.7 ranks the European countries according to the period in which heart transplantation was started.

Figure 6.7
Start of heart transplant programmes in Europe

Starting period	Countries
Pioneers 1968–70	France United Kingdom Germany Switzerland
Early adopters 1979–84	United Kingdom★ Austria Germany★ Sweden Switzerland★ Netherlands Belgium Spain Norway
Late adopters 1985–8	Italy Portugal Ireland Turkey Finland
Not yet started or only very recently started	Denmark Greece Luxembourg

★) Resumed transplantation after moratorium 1970–8

Ten out of the 18 countries started heart transplantation immediately after 1984, some more slowly, and Greece and Denmark only in 1990, leaving only Luxembourg as the member state which has not yet started at all. Although the number of patients on the waiting list for transplantation is growing steadily, there was in most countries no significant shortage of donor hearts in 1988, and in fact a sizeable number of available organs was not used at all, because of a lack of suitable recipients. This situation is now changing rapidly and waiting lists and waiting time for heart transplantation are increasing everywhere, especially for the non-urgent group of patients.

The development of heart transplantation in each European country is shown in Table 6.12, which gives activity before and in 1985 and in 1988, and gives the cumulated number of transplants over the period 1968–88.

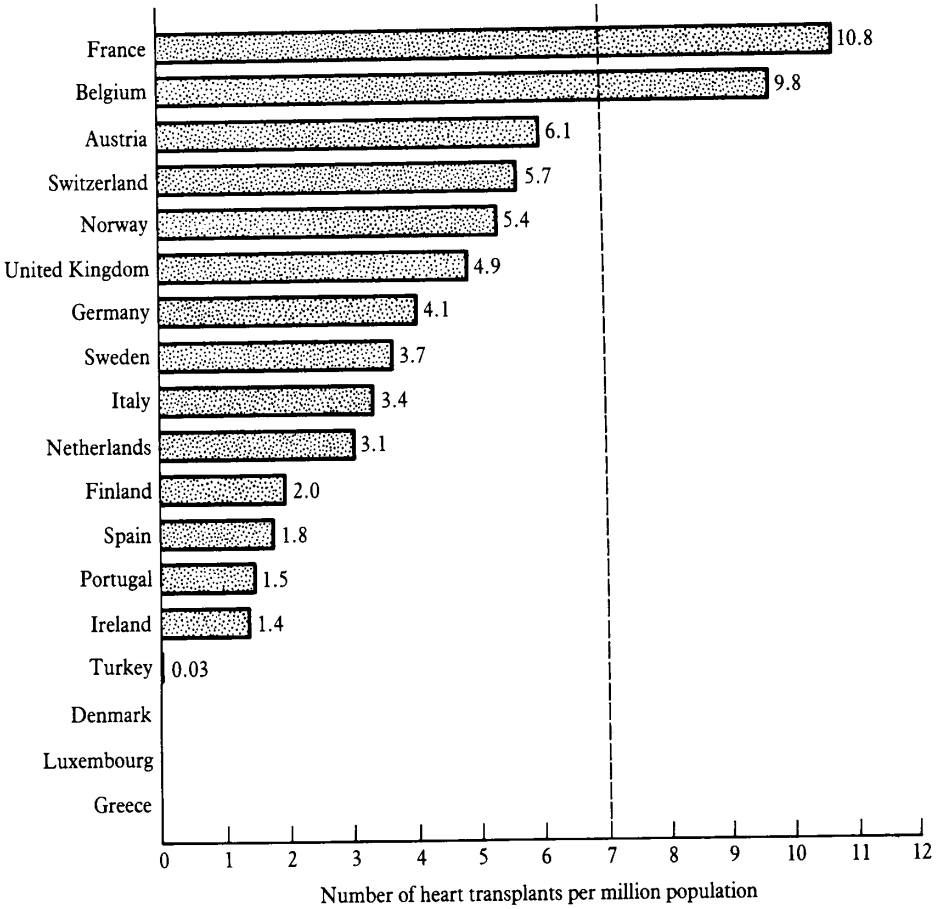
Table 6.12
Development of heart transplantation in European countries, 1968–88

Country	Total pre-1985	1985	1988	Cumulated 1968–88
Denmark	–	–	–	–
Germany	73	71	250	783
Netherlands	1	10	46	123
Belgium	14	20	96	248
Luxembourg	–	–	–	–
France	233	147	600	1779
United Kindgom	269	137	278	1104
Ireland	–	1	5	18
Spain	–	22	72	199
Portugal	–	–	15	24
Italy	–	16	196	429
Greece	–	–	–	–
Total Europe I (EC)	590	424	1558	4707
Sweden	1	4	31	44
Norway	8	11	23	78
Finland	–	2	10	23
Switzerland	19	8	37	105
Austria	5	3	46	135
Turkey	1	–	2	3
Total Europe II (non–EC)	34	28	149	388
Total Europe (I + II)	624	452	1707	5095

Early experience is shown to be concentrated in France, the UK and FRG. Over-all growth came after 1985, with most countries doubling or even tripling the number of transplants in the next four years. Rather impressive is the record of France, where heart transplantation has grown by 400 per cent since 1985. The development in the UK (one of the pioneer countries) in the same period shows a much more restricted diffusion of transplant technology, as the result of a deliberate policy to limit the number of centres and the funds devoted to transplantation. France, by contrast, has actively promoted the diffusion of heart transplantation and the proliferation of transplantation centres – facilitated by the fact that reimbursement of heart transplantation was never an issue with the insurance agencies.

The position of each of the European countries is illustrated differently in Figure 6.8, in which the rate of heart transplants per million population for the countries in 1988 is given.

Figure 6.8
Heart transplantation rate in European countries in 1988 (ranking according to number of transplants per million population)

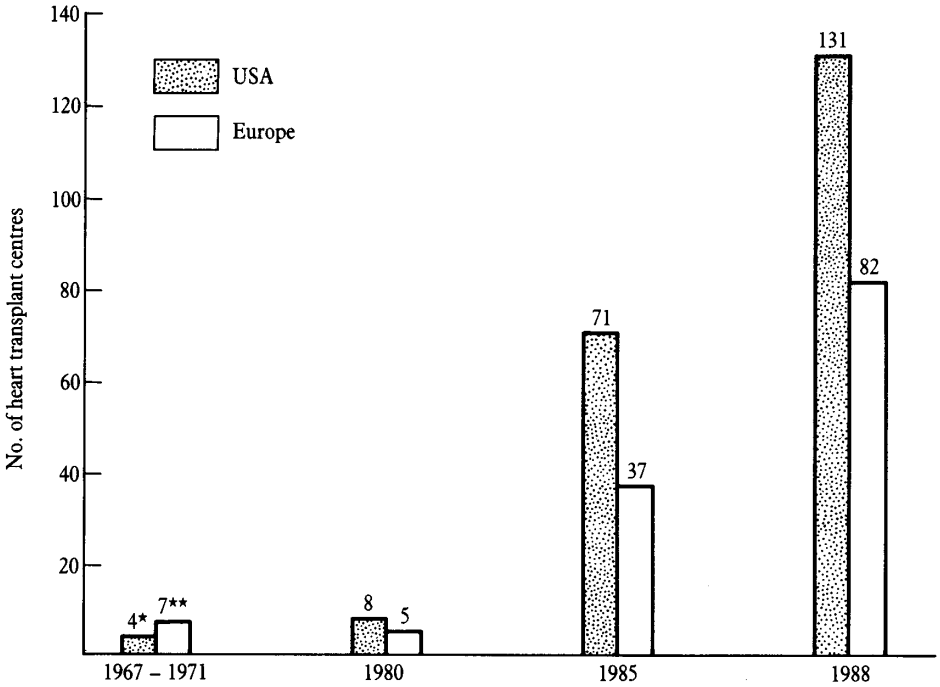


There is remarkable variation in activity between the countries: France, with the highest rate pmp, performs seven times as many transplants as Ireland. If 7 heart transplants pmp (as indicated in the Figure) is taken as a reasonable estimate for the 'need' in 1988, which is met in the USA, we see that in Europe only France and Belgium meet this target.

The proliferation of heart transplant centres in Europe

There has been a growth in numbers of transplant centres both in Europe and the USA, but the difference between the continents in this respect is striking. In 1988 the USA had 131 recognised heart transplant centres, on average one per every 1.7 million population. In Europe there were 82 centres, with an average of 4.9 million people per centre (Figure 6.9). This is partly due to the fact that in the USA coronary by-pass surgery is performed in a large number of relatively small hospitals, which also became interested in heart transplantation.

Figure 6.9
The number of heart transplant centres, Europe and USA, 1967–88



Sources: US General Accounting Office (GAO) 1989
Int. Heart Transplant Registry 1989

* Three centres discontinued their programme after 1970 and resumed after 1980

** Six centres discontinued their programme after 1970 and resumed after 1979

However, of the 131 hospitals registered with the United Network for Organ Sharing (UNOS) as transplant centres, 22 performed no transplants in 1988, and fewer than a quarter of the 131 centres met the quality criterion of at least 12 transplants a year proposed by the public and private financing agencies in 1987. As a result, only 23 centres had heart transplantations fully

reimbursed by Medicare in 1988. This has led to heated debate on the quality of transplants in smaller, less experienced centres.

Table 6.13 shows the proliferation of heart transplantation centres in European countries in 1988.

Table 6.13
The number of heart transplant centres in European countries and USA, 1988

Country	Centres	Mill. pop. per centre	Average no. of HTX per centre
Denmark	0	0	0
W. Germany	13	4.6	19
Netherlands	2	7.3	23
Belgium	6	1.6	16
Luxembourg	0	0	0
France	26	2.1	23
United Kingdom	5	11.3	55
Ireland	1	3.6	5
Spain	5	7.7	14
Portugal	4	2.5	4
Italy	9	6.4	22
Greece	0	0	0
Sweden	3	2.7	10
Norway	1	4.2	23
Finland	1	4.9	10
Switzerland	3	2.2	12
Austria	3	2.5	15
Turkey	1	52.8	2
USA	131	1.7	12★

★ 22 out of 131 centres did not perform any transplant in 1968.

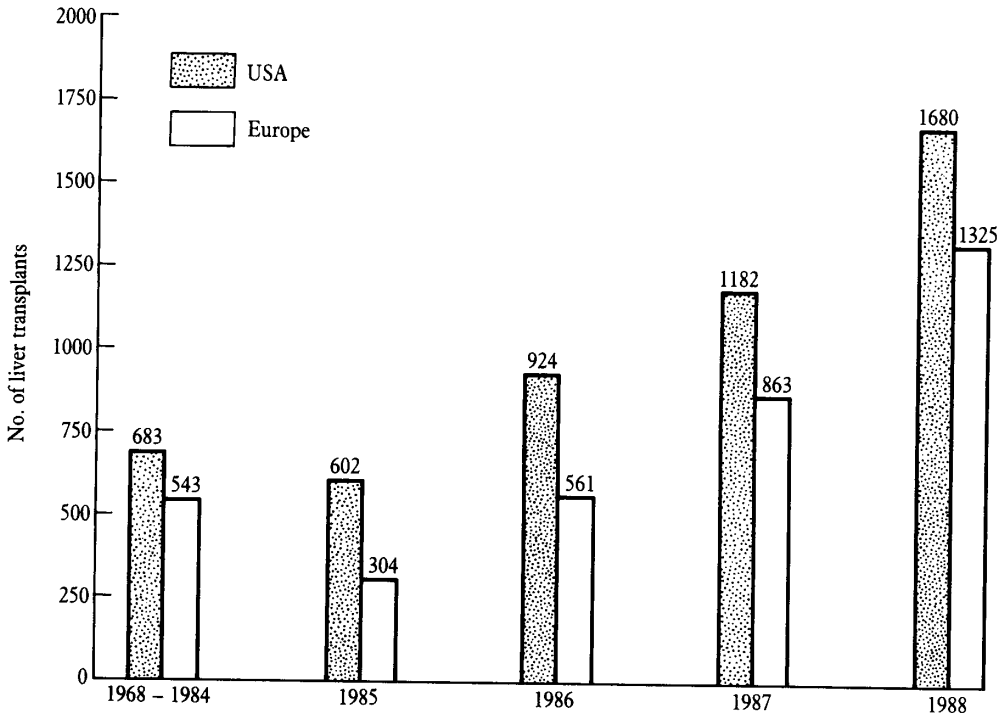
The number of transplant centres is generally larger in the group of countries with the highest transplant rate pmp: France, Belgium, Austria and Switzerland. The difference between France and the UK is striking, despite their similar populations, scientific interest in transplantation and early start in clinical heart transplantation. Their transplant programmes have developed quite differently because of different policies in health care and financing.

THE DEVELOPMENT OF LIVER TRANSPLANT PROGRAMMES IN EUROPE, 1968–88

The early development of liver transplantation is somewhat similar to that of heart transplantation. The USA took the lead after the first clinical transplant in 1963 (Starzl, Denver), and Europe followed, with the centre in Paris

performing the first European transplant in 1964. Real success in liver transplantation came several years later when in 1967 Starzl (moved to Pittsburgh) reported good survival,[71] with Europe following again in 1968 (Calne in Cambridge).[72] Until about 1980 developments in both the USA and Europe were similar in size and intensity. After 1980, however, the USA started to expand its programme of liver transplantation (with Pittsburgh as the most prominent centre) and grew faster than Europe, both in number of transplants and number of centres (Figure 6.10).

Figure 6.10
Development of liver transplantation in Europe and USA, 1968–88



Cumulative number of liver transplants 1968 – 1988: USA 5071, Europe 3596

After an early start, the USA has stayed well in the lead over Europe, although the USA and Europe have continued to expand liver transplantation at about the same rate. The gap between the USA and Europe is even larger in terms of the number of transplants pmp: the USA reached 7.3 transplants pmp in 1988, Europe only an average of 3.2 pmp.

The start of liver transplant programmes in Europe

Liver transplantation was pioneered in the same European countries (France, UK, FRG, Belgium, Figure 6.11) as embarked first on heart transplantation (Figure 6.7). Most countries in southern Europe made a later start than the north and the west. Denmark, like Greece, started this service only in 1990.

Figure 6.11
Start of liver transplant programmes in Europe

Starting period	Countries	
Pioneers	W. Germany	
1963–70	France	
	United Kingdom	
	Belgium	
Early adopters	Austria	Switzerland
1971–83	Netherlands	Finland
	Spain	Turkey
Late adopters	Norway	Ireland
1984–8	Sweden	Portugal
	Spain	Turkey
Very late adopters	Denmark	
1990	Greece	
Not yet started	Luxembourg	

Table 6.14 shows the number of liver transplants in each of the European countries before and during 1985 and in 1988.

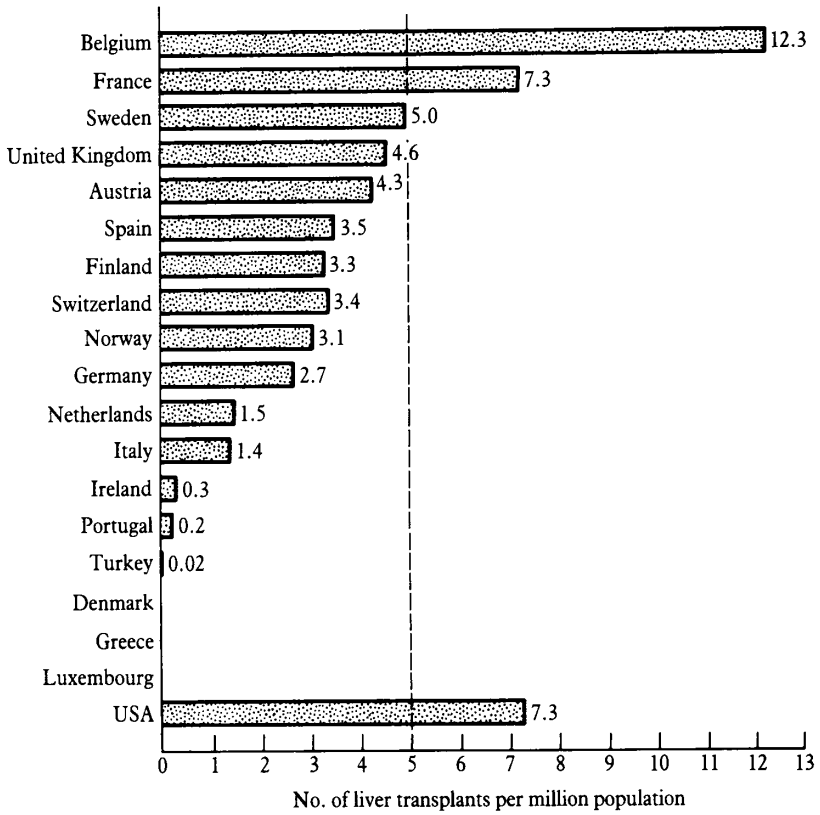
Table 6.14
Development of liver transplantation in European countries 1968–1988

Country	Total pre-1985	1985	1988	Cumulated 1968–88
Denmark	–	–	–	–
W. Germany	167	52	166	591
Netherlands	41	10	22	112
Belgium	10	26	121	300
Luxembourg	–	–	–	–
France	72	57	409	912
United Kingdom	194	88	261	845
Ireland	–	2	1	8
Spain	13	4	136	258
Portugal	–	–	2	3
Italy	8	5	81	167
Greece	–	–	–	–
Total Europe I (EC)	505	244	1199	3196
Sweden	1	12	42	100
Norway	2	2	13	29
Finland	2	4	16	38
Switzerland	2	2	22	42
Austria	31	40	32	190
Turkey	–	–	1	1
Total Europe II (non-EC)	38	60	126	400
Total Europe (I + II)	543	304	1325	3596

European experience in liver transplantation before 1984 was concentrated in the UK, France and FRG, while a fourth centre in the Netherlands (Groningen) also made a prominent contribution. After 1984, the number of transplants in France almost doubled every year, but the growth rate of Belgium and Spain is also impressive. In the UK, Belgium and Spain, the liver transplantation scene is dominated by a single centre performing the majority of transplants (Cambridge, Brussels and Barcelona). In France, on the other hand, a fairly large number of centres contribute to the high volume of transplants.

Figure 6.12 shows the number of liver transplants pmp in each country in 1988, ranked from the highest to the lowest rate.

Figure 6.12
Liver transplantation rate in European countries in 1988
(ranking according to number of transplants per million population)



If we compare these data with Figure 6.8 on the diffusion of heart transplantation, several similarities are evident:

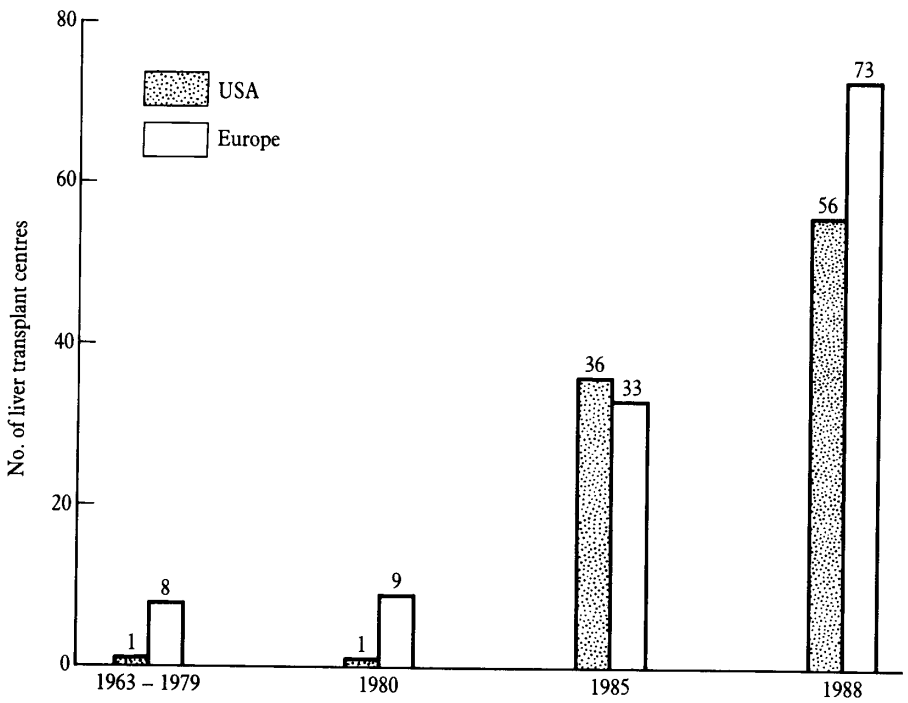
- Belgium and France are leaders in both kinds of organ transplantation in Europe
- Four countries appear in the first six positions in both lists
- The two transplantation rates pmp are of the same order of magnitude, the heart transplantation rate usually being somewhat larger. The exception here is Spain, where the liver transplant rate is twice the size of the heart transplant rate. (In the USA, heart and liver transplant rates are almost identical.)

If we take the need for transplants in 1988 to be at least 5 pmp, the Figure shows that only three countries in Europe meet this mark – Belgium, France and Sweden – as does the USA.

The proliferation of liver transplant centres in Europe

The pattern of diffusion of liver transplantation is reflected in the proliferation of the number of transplant centres. Up to 1983 liver transplantation was considered in most countries an experimental procedure which should be undertaken only in large centres with long-standing experience in kidney transplantation. Consequently there were only a handful of transplant centres world-wide at that time. Figure 6.13 illustrates early developments and the surge in liver transplantation after 1983.

Figure 6.13
The number of liver transplant centres in Europe and USA



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

For over 15 years, the number of liver transplant centres in both the USA and Europe remained constant. During this period of experimental clinical development, activity in the USA was concentrated in a single centre (first Denver, and later Pittsburgh, with Starzl as the pioneer). In the same period liver transplantation was developed in a few prominent European centres (Cambridge, Paris, Munich, Hannover, Lyon and Groningen). The improvement in surgical technique and immunosuppressive therapy, largely due to the introduction of cyclosporin in 1980, led to the 'maturing' of liver transplantation as a clinical modality in the early 1980s. This is reflected in the rapid increase in the number of liver transplant centres in the USA, followed more slowly by Europe. Between 1985 and 1988, the number of centres in

Europe doubled, largely because liver transplantation got off the ground in southern Europe. After 1988 the growth rate in the USA declined because of the shortage of donor organs, but also as a result of the UNOS policy to limit the number of centres doing less than 12 transplants a year.

Table 6.15 gives the number of liver transplantation centres in each European country in 1988.

Table 6.15
The number of liver transplant centres in European countries and USA, 1988

Country	Centres	Mill. pop. per centre	Average no. of LTX per centre
Denmark	0	0	0
W. Germany	11	5.5	15
Netherlands	2	7.3	11
Belgium	3	3.3	40
Luxembourg	0	0	0
France	26	2.1	16
United Kingdom	6	9.4	43
Ireland	1	3.6	1
Spain	4	9.7	34
Portugal	2	5.1	1
Italy	6	9.5	13
Greece	0	0	0
Sweden	2	4.1	21
Norway	1	4.2	13
Finland	1	4.9	16
Switzerland	4	1.6	5
Austria	3	2.5	11
Turkey	1	52.8	1
USA	56	4.1	30

Striking is the fact that the proliferation of liver transplant centres in Europe is similar to that in the USA, unlike heart transplantation where the USA leads Europe two to one. Several countries in Europe have a much greater number of liver transplant centres per head of population than the USA, with Switzerland in the lead with one centre for every 1.6 million people. Switzerland, Austria, France and Belgium are the leaders in liver transplantation in Europe in this respect. The Scandinavian countries, The Netherlands and the UK all have the policy of creating national referral centres for liver transplantation and discouraging the proliferation of centres.

Thus, the average number of transplant centres in each country cannot be taken as an indication of the level of activity: as in heart transplantation, most countries have one or two large centres that dominate and perform the majority of transplants.

THE NEED FOR HEART AND LIVER TRANSPLANTS IN EUROPE IN 1990

The pattern of diffusion of heart and liver transplantation in Europe and the USA can be summarised by comparing the actual number of transplants with the estimated need (Table 6.16).

Table 6.16
The need for heart and liver transplants in Europe and the USA in 1990

Region	Situation 1988		Needed 1990	
	pmp	abs	pmp	abs
EC countries:				
– heart Tx	4.8	1558	10	3230
– liver Tx	3.7	1199	7	2260
All Europe:				
– heart Tx	4.2	1707	10	4070
– liver Tx	3.2	1325	7	2850
USA:				
– heart Tx	7.2	1647	10	2300
– liver Tx	7.3	1680	7	1610

Here, the need for heart transplants has been arbitrarily set at 10 pmp, and for liver transplants at 7 pmp. Most experts would consider these to be conservative estimates, some putting the figures at 15–25 pmp, but they appear realistic in terms of the actual situation.

The contrast between the EC/Europe and the USA is clear: the USA has progressed significantly in meeting the 'need' for transplants in its population, while Europe is still far from reaching the targets. However, Americans see no reason for complacency: there is a public as well as professional demand for further expansion of the transplant programme, which is blocked by poor availability of donor organs. In Europe the number of heart and liver transplants is still growing, especially in the southern European countries that made a late start. The problem here is not a shortage of donor organs but the necessity of overcoming infrastructural problems.

In most European countries the available number of donor organs is not (yet) the major problem, since the proportion of kidney donors who actually become multi-organ donors is relatively low and there is still scope for improvement without increasing the number of donors.

SOME GENERAL CONCLUSIONS

1 Although Europe contributed to the early development of experimental and clinical transplantation in much the same way as the USA, the latter has taken the lead in developing heart and liver transplantation as a regular health service. Consequently the diffusion of heart and liver transplantation in the 1980s was much higher in the USA than in Europe, but at the beginning of the 1990s Europe is catching up.

2 In Europe, heart and liver transplantation started early in those countries with a long-standing tradition of scientific interest in transplantation and immunology: France, UK and FRG.

3 However, these were not necessarily the countries that developed the largest clinical programmes. At present Belgium, Austria and Switzerland (together with France) are in the front rank, while the FRG and the UK have more modest positions.

4 The prominent position of the Scandinavian countries in the development of kidney transplantation programmes was not repeated in heart and liver transplantation. In most Scandinavian countries heart and liver transplantation started rather late, and the expansion has been moderate (mostly as the result of a deliberate health service policy). Denmark only recently (1990) started heart and liver transplantation programmes.

5 In general, there is a time lag in developments in transplantation between northwestern European countries and the southern region. However, some countries in the south (Spain, Portugal, Northern Italy) are making rapid progress.

7 FACTORS AFFECTING THE DIFFUSION OF ORGAN TRANSPLANTATION IN EUROPE

7.1 THE TYPE OF HEALTH CARE SYSTEM

Health care systems may be divided into three categories:

Public health care systems in which the responsibility for the delivery, planning and financing of health care rests with central and local governments. It is financed mainly from general taxation, although premiums from social security and private contributions from patients may also play a minor role.

Social security health care systems are mainly financed from insurance funds within a system of social security. Membership of sickness funds is usually compulsory, and the services to be reimbursed are laid down in statutes. There may be a component of voluntary, private insurance above a certain income level. The responsibility for public preventive health care rests with the national or local health care authorities, which may also be involved with the planning and regulation of health care facilities.

Other systems are usually hybrids of public health care, social security and private health care.

In any of these systems there may be private initiatives in the delivery of health care. This private sector may or may not be reimbursed from the national system, may or may not be subject to planning regulations and may or may not be for profit. The extent to which the private delivery of health care plays a role in the total system may also vary widely: in some countries the private sector is negligible but in others it is large and in active competition with the national system.

On the role of the private sector a remark should be made about the situation in the FRG, where there exists a system of independent physician specialists working part-time outside the hospitals (niedergelassene Fachärzte). Although these doctors are free to use and invest in medical technologies, they operate within the social security system with its fixed tariffs and negotiated set fees. For this reason they cannot be equated with the for-profit private clinics in a number of other countries.

A further, more general remark is also in order: although it is generally true that private institutions and practitioners are free to use and invest in any kind of technology (which has led in some countries to an explosive diffusion and over-use), this is not so for organ transplantation. Most health care systems restrict this practice to the public hospitals either through legislation, requirement of certification of approval, or reimbursement restrictions. In Europe, transplantation in private hospitals is currently only permitted and performed in the UK, Spain, Portugal and Switzerland (and Turkey). However, this results in only a very small number of transplants. The health care systems in Belgium and the FRG permit transplantation in private hospitals in principle, but none of these hospitals actually perform the procedure. The over-all

conclusion must therefore be that the private sector exerts no significant influence on the diffusion of this technology.

Table 7.1 shows the number of kidney, heart and liver transplants per million population in 1988 alongside the type of health care. No general conclusion can be drawn: high and low volumes of transplants per million population occur in all systems.

Table 7.1
Number of organ transplantations per million population (1988) versus type of health care system

Country	Health system	Private sector contribution	Transplants per million population
Sweden	Public	Negligible	51.4
Norway	Public	Negligible	48.9
UK	Public	Growing	41.0
Finland	Public	Negligible	37.1
Spain	Public	Growing	31.5
Denmark	Public	Negligible	28.6
Ireland	Public	Growing	23.3
Portugal	Public	Growing	21.5
Italy	Public	Considerable	16.3
Greece	Public	Large	9.1
Turkey	Public	Considerable	5.3
Belgium	Soc security	Growing	60.4
Austria	Soc security	Small	51.3
France	Soc security	Large	50.6
FRG	Soc security	Considerable	35.3
Netherlands	Soc security	Negligible	33.2
Luxembourg	Soc security	Negligible	15.0
Switzerland	Pluralistic	Considerable	41.1

7.2 HEALTH CARE EXPENDITURE PER CAPITA

Table 7.2 ranks countries according to the health care expenditure per capita with the total number of transplants pmp in 1988.

Table 7.2
Health care expenditure per capita (US$, in 1988) and the diffusion of organ transplantation

Country	Health care expenditure	Total transplants pmp in 1988
Switzerland	1217	41.1
Sweden	1195	51.4
France	1039	50.6
FRG	1031	35.3
Norway	1021	48.9
Netherlands	984	33.2
Luxembourg	968	15.0
Austria	903	51.3
Finland	900	37.1
Belgium	826	60.4
Denmark	800	28.6
Italy	764	16.3
UK	711	41.0
Ireland	549	23.3
Spain	486	31.5
Portugal	310	19.8
Greece	245	9.1
Turkey	140	5.3

The general conclusion can be drawn that countries with a high per capita expenditure on health care have a higher use of expensive technologies such as organ transplants than those with a more moderate expenditure, but this does not explain why countries that do not belong to the group of highest spenders nevertheless are high in organ transplantation (Belgium, Austria). The apparent low use of organ transplantation in Luxembourg is a distortion of reality: residents of that country get kidney, heart and liver transplants in neighbouring countries, particularly Belgium.

7.3 INFRASTRUCTURE AND LEGISLATION

Transplantation, especially of kidneys, could not have developed into an established health service without a considerable degree of organisation. The use of the artificial kidney created a large population of patients on haemodialysis who were also candidates for kidney transplantation. The improving techniques for the preservation of donor kidneys and the expanding knowledge of histocompatibility provided the keys to a greater use of cadaveric organs. The very fact that the early pioneers of kidney transplantation were obliged to look for ways of expanding the number of available organs led to the establishment of organisations to procure and exchange kidneys on a regional, national and even international basis.

As the number of transplants grew, the need was felt in many countries for

specific legislation to cover the legal and ethical aspects of organ donation and removal.

Most European countries have over the past 25 years developed an infrastructure consisting of:

- centres of excellence in organ transplantation, transplant immunology and tissue typing
- regional or national organisations for donor procurement (using transplant coordinators) and regional, national or international agencies for organ exchange
- legislation on organ removal and donation and/or an established professional code of good practice.

The presence of such an infrastructure has been of great importance also for heart and liver transplantation, which because of the need for multiple organ procurement, matching, transport and implantation within very short periods is possible only in a well-organised setting.

7.3.1 Infrastructure for the procurement and exchange of donor organs

Infrastructures for the procurement and exchange of donor organs have usually been developed in countries before any legislation took place. The first serious proposal to start national and international cooperation in the exchange of donor kidneys was put forward during the third Histocompatibility Testing Workshop in Turin in 1967. The promoters were Jean Dausset (France) and Jon van Rood (The Netherlands), both distinguished pioneers of immunology and histocompatibility who had played a crucial role in developing tissue matching on the basis of the HLA system. The crux of the proposal was that all cadaveric donor organs should be matched against a list of registered and tissue-typed potential acceptors in order to find the best possible acceptor for a given kidney. The larger the pool of recipients on the waiting list the better the chance of a fully compatible match. The basic idea of this proposal was supported by most of the participants at the meeting, but the time was not yet ripe for a truly European exchange organisation. International cooperation was accepted by the five countries which participated in the Eurotransplant Foundation beginning in 1967. Other countries followed with organisations based on national exchange. Coordinating arrangements within the countries varied (Table 7.3).

Table 7.3 shows that all European countries have now made arrangements for the procurement and exchange of donor organs, the countries in the south doing so almost ten years later than in the north and west. In general this has resulted in a considerably lower number of donors and kidneys available.

Table 7.3
Organisations for donor procurement and organ exchange

Country	Organ exchange agency	Donor procurement
Netherlands	Eurotransplant (1967) logistic centre, Leiden University Hospital	7 regional coordinators
FRG	Eurotransplant	Local coordinators
Austria	Eurotransplant	Local and regional coordinators
Belgium	Eurotransplant	Local coordinators
Luxembourg	Eurotransplant	1 national coordinator
France	France-Transplant (1969) centre in Paris, 7 regional organisations	1 national, 7 regional, 28 local coordinators
Switzerland	Swiss Transplant (1969), centre in Geneva	No coordinators
Denmark	Scandia Transplant (1969), centre in Aarhus	Regional coordinators
Sweden	Scandia Transplant	Regional coordinators
Norway	Scandia Transplant	Coordinator at national centre
Finland	Scandia Transplant	Coordinator at national centre
UK	UK Transplant Service (UKTS 1972)	2 national coordinators for hearts, regional coordinators for other organs
Ireland	UKTS provides services	Regional coordinator
Italy	North Italy Transplant (NITp 1976), centre in Milan; Associazione Interregionale Trapianti (AIRT), centre in Bologna; Sud Italia Transplant (SIT), centre in Rome; Coordinamento Centro Sud Trapianti (CCST 1987), centre in Rome	Local and regional coordinators Regional coordinators Local coordinators Regional and local coordinators
Spain	Catalunya Transplant, centre at Barcelona; Hispano Transplant for rest of Spain, centre at Madrid	Regional coordinators Local and regional coordinators
Portugal	Luso Transplante (1986), centre at Lisbon	Local coordinators
Turkey	Turkish Transplantation and Burn Foundation (1980), centre in Ankara	Local coordinators
Greece	Hellenic Transplant Service (YSE, 1985), centre in Athens	National coordinator

All these organisations now come more or less directly under the public health service and also receive funding from that source, even though several started as private initiatives. The exception is Eurotransplant, which was founded on the initiative of transplant doctors, dialysis centres and tissue typing centres and has remained independent of the public health service and government. However, those that come under the control of the public health services do not have common policies. France-Transplant, Scandia Transplant and the UKTS, although publicly funded, are run as autonomous organisations and have a professional management. Italy has four autonomous exchange organisations which cooperate to a certain extent but base their policies on regional rather than national issues. In Turkey there exists a national exchange organisation alongside private, non-profit procurement agencies which follow their own policy. In the other countries the exchange organisations are run directly by the ministries of health.

To highlight the variety of arrangements in this field we will discuss a few of these organisations in greater detail.

Eurotransplant

The Eurotransplant Foundation was legally founded on 12 May 1969 and has its central office at the University Hospital, Leiden (The Netherlands). It coordinates organ exchange between Germany, Austria, Belgium, Luxembourg and The Netherlands. It was and still is a private organisation, funded by the insurance agencies in these countries on a 'fee for service' basis. The services in question are provided by Eurotransplant to centres which participate on a voluntary basis. They include maintenance of a central waiting list for all potential recipients of kidneys, heart, liver, pancreas and typed corneal grafts, with central computerised matching of available donor organs to recipients on the basis of HLA and ABO characteristics. Special services are offered for highly immunosuppressed kidney patients, high-urgency kidney, heart and liver recipients and paediatric patients. Eurotransplant also arranges removal and transport of organs and the corresponding financial aspects. Eurotransplant does not coordinate the actual organ procurement in the participating countries; it is the responsibility of national agencies.

Eurotransplant has managed to hold a monopoly position in all the participating countries, without any competition arising. This must mean that Eurotransplant offers a quality product in the rapidly changing field of transplantation medicine which others cannot improve on. The rules and procedures within Eurotransplant, to which all centres voluntarily subscribe, are continuously negotiated in a democratic fashion. They include rules on organ sharing (priority for completely compatible kidney match, for highly immunised patients, and for recipients on high-urgency codes) and on balancing the import and export between countries. Eurotransplant has therefore been able to survive the trend towards individualisation and nationalisation of organ procurement. A fully computerised information exchange network between transplantation centres is now being developed in order to continue these services into the 1990s.

Results of this international approach are that, in 1989:
- the exchange rate for donor kidneys was 58 per cent
- the total waiting list for kidneys was 9445
- the number of available kidneys was 3014
- the number of kidney transplants performed was 3072
- the average cold ischaemia time was 23 hours
- the proportion of multi-organ donors was 48 per cent
- the number of heart transplants was 521
- the number of liver transplants was 499
- survival results of transplantation were excellent.

Italy

The situation in Italy, with four autonomous procurement and exchange organisations in one country, is the very opposite of Eurotransplant. The oldest organisation is NITp (1976), which provides services to the northern provinces. AIRT serves a well-defined area, but SIT and CCST overlap, and both have their central office in Rome (Figure 7.1).

The result of this complexity is that large differences exist between the regions (data for 1988):

	Donor procurement rate
in NITp	8.6 per million population
in rest of Italy	4.2
average rate for Italy	5.5

	Kidney transplant rate
in NITp	18.4 per million population
in rest of Italy	8.5
average rate for Italy	11.4

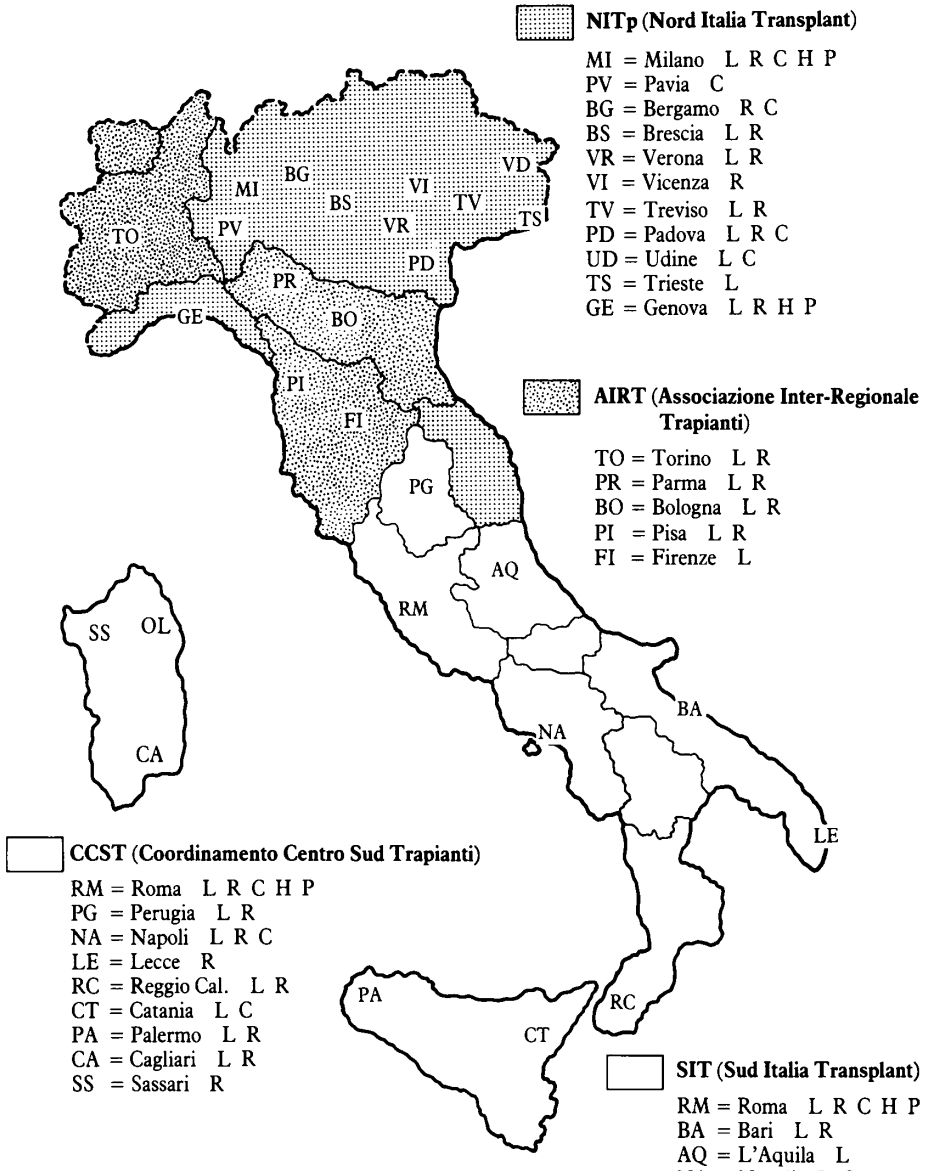
In heart transplantation some measure of cooperation has been reached between the nine active centres, each centre being assigned its own organ retrieval area. This policy has been moderately successful. However, most of the nine centres are too small, performing fewer than 15 heart transplants per year.

The efforts at coordination have been most successful in liver transplantation, a national programme with six centres supervised by NITp being started in June 1986. There are now plans for a national paediatric transplant programme.

Logistic problems for organ procurement in Italy are manifold, only a few hospitals being actively engaged, mainly because ICU staff are not interested, there are insufficient means of transport and information technology is underdeveloped. Many Italian patients are registered on more than one waiting list.

Several organs are sent abroad without anyone checking whether they could be used in Italy.

Figure 7.1
Transplant organisation in Italy



L = Tissue typing laboratory, C = Cardiac transplantation, R = Renal, H = Hepatic, P = Pancreatic transplantation.

Spain

The situation in Spain somewhat resembles that in Italy. The many local and regional organ procurement agencies in the nine autonomous provinces cooperate loosely under a national scheme run by the ministry of health in Madrid, but there is little central guidance: it is mostly the local or regional transplant centres that supervise donor procurement for the benefit of their own programme. Waiting lists are not amalgamated and there is little sharing of organs between provinces.

An exception is Catalonia (Generalitat de Catalunya), population 6 million, which has organised its organ procurement on a national basis since it was given autonomous status in 1982. Catalunya Transplant also cooperates closely with France-Transplant. In Barcelona, where half the population lives, there are six transplant centres, three within the public health service and three private centres under contract to the health service. By means of an intensive education campaign and with the help of active local transplant coordinators, Catalonia has now reached more than 40 transplanted kidneys per million population, a rate similar to that in Scandinavia and Austria. For the rest of Spain this rate is 24.

For heart and liver transplantation the situation in Spain is less problematic: a voluntary national exchange programme for extra-renal organs, coordinated through the office in Barcelona, has been in existence since May 1987. This programme aims for a central waiting list, central reporting of donors, and efficient and just allocation of organs over the centres. The policy has proved feasible and resulted in one year in a considerable increase of extra-renal transplants:

	1987	*1988*
donors reported	113	267
heart transplants	29	69
liver transplants	31	121

7.3.2 Legislation on organ procurement and transplantation

Specific legislation concerning the removal and therapeutic use of human organs and tissues dates from the early 1960s, when corneal transplantation had become more or less established but kidney transplantation had only just started. The first country to produce legislation was the UK with its Human Tissue Act of 1961, followed by Italy, Scandinavia and France in the late 1960s and early 1970s. The aim was to provide a legal basis for the protection of potential donors, to secure the right of self-determination by the person concerning the use of his organs and tissues after death and to clarify the responsibilities and rights of doctors wishing to remove and transplant organs. It also aimed at setting ethical limits on the use of living donors, minors and other legally incapacitated persons.

The Council of Europe (CE) has made an important contribution to this legislative process during the past 15 years. In 1978, after a meeting of the national ministers of health in Strasbourg, the CE issued recommendation

(78)29, 'Harmonisation of legislations of member states relating to removal, grafting and transplantation of human tissues'. The CE recommended (Article 10) that 'no removal must take place when there is an explicit or presumed objection on the part of the deceased, in particular taking into account his religious and philosophical convictions. In the absence of the explicit or implicit wish of the deceased the removal may be effected.' The CE asked member states 'to conform their laws to the rules annexed to this resolution or adopt provision conforming to these rules when introducing new legislation.' The resolution therefore promoted legislation based on the opting-out principle, ie organs may be removed if there is no explicit objection on the part of the donor, expressed in his lifetime. Seven countries have since introduced new legislation based on this principle, but a smaller number of countries have introduced legislation stating that organs may be removed only when the deceased has given explicit consent during his lifetime, and some countries have produced no legislation, regulating organ removal on the basis of a code of practice, usually based on the opting-in principle and requiring the consent of next of kin.

In 1987 the ministers of health of the CE member states again convened, in Paris, on the subject and brought forward new recommendations. Article 10 was rewritten to state that 'a removal from a dead person may take place only when there is consent on the part of the deceased.' It was emphasised (Articles 4.1 and 4.2) that 'the contracting member states shall take the necessary measures for determining easily and clearly the wish of the deceased.' This time the recommendations did not promote the opting-out principle but took the position that member states could use either the opting-in or opting-out principle provided the explicit wish of the deceased was determined and respected. This change of attitude was brought about by the Swedish and Dutch delegates.

There is now a wide spectrum of legislative systems concerning organ removal and transplantation in Europe, see Table 7.4.

Table 7.4
Legislative systems on organ removal and transplantation in Europe

Country	Legislation	Principles
UK	1961: Human Tissue Act	Concerns all removals, not only for transplantation. Deceased must have given explicit consent.
	1989: Removal of Organs from Living Donors	No commercial use of organs; living donors should give informed consent; all organ removals must be registered
Italy	1967: Law 458, on the transplantation of kidneys from living donors	Consent from living donors
	1957: Law 519, revised 1975, on the removal of body parts from deceased persons	Opting-out principle for deceased donors

(contd)

Table 7.4 contd
Legislative systems on organ removal and transplantation in Europe

Country	Legislation	Principles
Denmark	1967: Law 246, on the removal of all substances of human origin	Opting-out for deceased, consent from living donors
	1990: Law 402 on the determination of death and transplantation	Same principles
Finland	1969: Board of Health circular 1454, on the use of tissues from deceased persons	Opting-out for deceased, consent from living donors
	1985: Act 355, on the removal of human organs and tissues for medical purposes	
Norway	1973: law 6, transplantation, autopsies and donation of bodies for scientific purposes	Opting-out for deceased, consent from living donors
Sweden	1975: Act 190, on transplantation	Opting-out for deceased, consent from living donors
	1988: change of law 190	Brain-death donors must have given explicit consent
Portugal	1976: law decree 553 concerning the use of all substances of human origin	Opting-out principle for deceased
France	1976: Act 76-1181 (Loi Cavaillet) on the removal of organs	Opting-out for deceased, consent from living donors
Turkey	1979: law 2238 on the removal, conservation and transplantation of human organs and tissues	Opting-in principle (consent or presumed consent) for deceased, consent from living donors
Spain	1979: Act on the removal and transplantation of organs	Opting-out for deceased, consent from living donors
Switzerland	1981: guidelines on medical ethics from the Swiss Academy of Medical Sciences	Opting-out principle for deceased donor
Austria	1982: Federal Act on the removal of human organs and tissues from deceased persons	Opting-out principle for deceased donor
Luxembourg	1982: Law on transplantation	Opting-out principle for deceased donor
Greece	1983: Act 1383 on the removal and transplantation of biological substances of human origin	Opting-out principle for deceased donor (but next of kin must agree); consent from living donors

(contd)

Table 7.4 contd
Legislative systems on organ removal and transplantation in Europe

Country	Legislation	Principles
Belgium	1986: Law on the removal and transplantation of all substances of human origin	Opting-out for deceased, consent from living donors
Netherlands	No legislation. Code of practice in operation	Opting-in for deceased, consent from living donors
FRG	No legislation. Code of practice in operation	Opting-in for deceased, consent from living donors
Ireland	No legislation. Code of practice in operation	Opting-in for deceased, consent from living donors

Table 7.4 shows that of the 18 countries in this study, 15 have effected legislation on the removal and transplantation of organs and tissues. The three countries which have not done this so far are planning to do so in the near future. Of the 15 legislative systems, 12 are based on the opting-out principle and three (UK, Sweden, Turkey) on the opting-in.

The Council of Europe has further initiatives to its credit which have influenced national legislation in the field of transplantation:

- the European Agreement (1974) on the exchange of tissue-typing reagents
- the 1979 recommendation on the international exchange and transport of human substances
- efforts to create a European organ sharing network for paediatric liver patients, highly immunised and urgent transplant recipients (1988). There are also plans to support a European bone marrow donor register.

Recently the World Health Organisation (WHO) has also been involved in harmonising legislation and the practice of organ transplantation. In 1987, resolution WHA 40.13 was adopted at the 40th World Health Assembly, calling for the development of guidelines for human organ transplantation, and in 1989 a second resolution (WHA 42.5) condemned the sale and purchase of human organs. Some draft guiding principles on human organ transplantation, particularly with regard to the prevention of commercial transactions with organs and tissues, were proposed and discussed at the 87th session in November 1990.

7.3.3 Legislative measures in individual countries

Belgium

Belgium adopted legislation on organ removal and transplantation in 1986 (implemented 1987), based on the opting-out principle. Belgian residents

must register any objection to removal of their organs after death with the municipal council, and these objections are held in a national register supervised by the ministry of health. To date, only 150,000 persons (1.5 per cent of the population) have registered objections.

The law allows a doctor to remove the organs of any deceased person after he/she has ascertained that the deceased has raised no objection during their lifetime; but the next-of-kin can still object when the doctor informs them of his/her intention.

This legislation, and the intensive public educational campaign which accompanied its implementation, had immediate effect: between 1987 and 1988 the number of donors and transplants almost doubled. The effect is now levelling off, but it has put Belgium in the front rank of organ transplantation in Europe.

Sweden

Sweden adopted opting-out legislation as early as 1975, when organ transplantation in Sweden was limited to kidneys and corneas. Hence there was no debate or practical problem concerning the definition and determination of death of the donor. These problems did arise when Swedish surgeons considered performing heart and liver transplants in the early 1980s, when they used organs from brain-dead donors maintained on respirators in the intensive care unit. Although the first transplants, in 1985/6, were successful there was much discussion over whether the removal of the organs was illegal.

Transplantation was halted until a new law, which established new criteria for legally accepted brain death, came into effect in January 1988. This new law required opting in, either previously on the part of the deceased or on the part of next of kin. The change from the opting-out to the opting-in principle was the political price for legal acceptance of the brain death criteria. However, this seems not to have affected public acceptance of organ transplantation, as the number of organs procured and transplants performed has not decreased.

Denmark

The Danish people too were confronted with the brain-death issue when the medical community considered introducing heart and liver transplantation in Denmark. However, in Denmark the reconciliation of medical and legal definitions of death has proved problematical.

A 1985 study of the feasibility of heart and liver transplantation led to a Bill proposed by the minister of justice which accepted the brain-death criterion. A Council on Medical Ethics was set up in 1987 and asked to initiate public debate on ethical aspects of heart transplantation, but before any conclusions had been drawn the Bill had to be dropped in view of a general election (May 1988). In 1988 the Council published its first report on 'The death criterion', proposing a combination of irreversible loss of brain function and cardiac arrest. This proposal gave rise to intense debate between the medical profession, ethicists and the lay public.

No unanimous position on a legislative proposal making possible the use of brain-death donors could be reached, so that heart and liver transplantation could not be performed at that time, although transplantations in Danish patients abroad were reimbursed by the public health service. The controversy over the brain-death criterion strongly affected public attitudes to kidney procurement for transplantation: the number of donors fell from 23.7 pmp in 1985 to 14.5 pmp in 1988, and the number of kidneys transplanted likewise fell from 230 in 1985 to 145 in 1988.

The Danish government finally resolved the controversy by adopting legislation (see Table 7.4) on 13 June 1990. However, part of the Danish public is still confused over the issue.

United Kingdom

Although the UK was the first country in Europe to introduce legislation on the use of human substances in general (Human Tissue Act 1961), the law did not refer specifically to transplantation and afforded no protection to living organ donors. In 1988 the British transplant community as well as the public were shocked to discover that in some private hospitals in London kidneys had been removed from unrelated living donors (poor Turkish peasants) in return for payment for their 'services'. The public outcry against this form of 'trafficking' in human organs threatened to harm the public's trust in organ procurement and transplantation, and a new law was rushed through Parliament in the summer of 1989 and implemented in the autumn. This Act made any payment for donor organs a criminal offence and spelled out rules to protect living donors in general. The doctors involved in the case of the Turkish peasants were severely punished.

Conclusion on legislation

The laws adopted in different countries concerning organ removal and transplantation have been of great importance in the diffusion of organ transplantation. In some countries heart and liver transplantation could be performed only after legislative change. Most countries have seen the number of organs procured and transplanted increase as the direct or indirect result of legislation, the main goal of which has been to protect donors, recipients and transplant doctors. But in many cases the law also facilitated reimbursement of organ removal and transplantation, set quality standards and contained other elements of planning and regulation.

One cannot conclude in general that opting in or opting out of post-mortem donation leads to better results in organ procurement, which is to a large extent dependent on the effectiveness of organisational arrangements, which varies greatly from country to country.

7.4 ROLE OF THE MEDICAL PROFESSION AND HEALTH AUTHORITIES

7.4.1 The introduction of kidney transplantation

The leading role in introducing kidney transplantation into every European country was undoubtedly played by the medical profession. The leading surgeons who performed the first kidney transplants headed teams with a strong interest in scientific research and wanted to push the treatment they could offer to the limit. Based as most of them were in university teaching hospitals, they took their own decisions on whether to offer a new, even experimental procedure to patients. This was before the days of hospital ethical committees, and often the hospital governors were not involved in or even informed of the decision.

Not one of the country reports claims that health service authorities, at central or regional level, were involved in the early days of kidney transplantation; in most countries the authorities remained completely aloof from transplantation and organ procurement and offered no financial or logistical support. This remained true for 10-15 years. Only when the prospects of kidney transplantation improved considerably through the development and use of effective immunosuppressive drugs, making the large-scale use of cadaveric donor organs feasible (about 1975), did the health authorities become interested, mainly because the number of dialysis patients was growing and putting a heavy burden on the health care budget. When it became evident that transplantation offered a more cost-effective solution to end-stage renal disease, governments began to promote organ procurement and support the doctors' initiative.

However, more substantial support usually came from private institutions: charities, patient and consumer organisations and research foundations. For example the Kuratorium für Heimdialyse (Council for Home Dialysis, KfH) in the FRG was formed to finance dialysis facilities, but when kidney transplantation became a clinical reality KfH also gave financial support to transplant centres, paying for extra staff and surgical and ICU facilities. Today the KfH plays a key role in the planning and financing of all transplantation activities in the FRG, being an intermediary between the transplant centres, the insurance companies and the government. It also promotes scientific research into transplantation through giving research grants.

In 1969, the Nordic Council of Ministers agreed to support the collaborative venture Scandia Transplant, initiated by tissue typing and transplant centres in Denmark and Sweden. The national boards of health in Scandinavian countries appointed a permanent committee on transplantation which later received a grant from the Nordic Council.

Also in 1969, the French pioneer of histocompatibility Jean Dausset started France-Transplant, a national network to promote organ procurement and organ exchange. The French health service authorities recognised its importance and supported its work. In 1978 France-Transplant acquired the status of 'public service organisation' and was funded by the government.

Similarly in Switzerland, Swiss Transplant started as a private initiative in 1969 and was funded by the health authorities in 1985; the United Kingdom Transplant Service was adopted by the NHS in 1972 after having started as a local initiative (the National Organ Matching Programme) in Bristol.

Another reason why health authorities became involved in kidney transplantation was the need for legislation (see previous section). However, except for The Netherlands and the Scandinavian countries, who introduced formal planning instruments to control the number of transplant centres in the mid-1970s, no country thought it possible to regulate the initiatives of doctors in starting new transplant centres. Indeed, in some countries this would have been regarded as highly improper – a curtailing of clinical freedom to prescribe any treatment that may be beneficial to the patient, and a limitation of the freedom of scientific research.

Another important factor, seldom mentioned in public, was the ambition of doctors and hospitals to offer transplantation as a service to attract patients to the hospital; each new transplant programme meant offering competition to established centres. This was the case especially in France, FRG and Belgium.

7.4.2 The introduction of heart and liver transplantation

Was the same picture repeated for these more radical forms of transplantation? Review of the country reports indicates that indeed a similar pattern is found: the decision to start such a programme was taken by an individual doctor or transplant team, in many cases without even the hospital administrators being involved. This was certainly the case during the first wave of heart transplantations beginning in 1967, following the example of Barnard. Then, after the voluntary moratorium in the 1970s, cardiac surgeons in Europe began again, once more without reference to health authorities, after hearing about the successful results at Stanford. Similarly, liver transplantation took off after favourable results were reported from the USA at the NIH Consensus Conference in 1983. By now, however, health authorities were prepared to react and were within 1–5 years trying to influence the speed of diffusion of heart and liver transplantation, by different means and with different degrees of success (Table 7.5).

Table 7.5 does not apply, however, throughout Europe: in those countries where the role of health authorities remained minimal it was the medical profession itself that tried to regulate the diffusion of heart and liver transplantation. Thus, in Italy transplant surgeons and hepatologists agreed on a national programme for liver transplantation at a consensus meeting in Milan in 1988, in Spain a similar approach resulted (1988) in a voluntary national exchange programme for extra-renal organs, and in Germany the Society for Organ Transplantation (Deutsche Arbeidsgemeinschaft für Organtransplantation) is attempting to reach consensus over the appropriate number and size of transplant centres.

Table 7.5
Roles of doctors and health authorities in organ transplantation

Phase	Kidney	Heart and liver
1	1960–70 start in most European countries. Initiative of the medical profession	1979–85 start in most European countries. Initiative of the medical profession
2	1970–8, growth of kidney transplantation through private initiatives	1985–present, consolidation and growth as the result of government support and collaboration between transplant centres
3	1978–present, consolidation and growth of programmes with gradual involvement and support from health authorities	

7.5 ROLE OF REGULATION BY HEALTH AUTHORITIES

Ever since health authorities have been faced with the need for cost containment in health care, confronted with growing needs and demands from the public that outpaced the available funds, they have been particularly concerned about expensive medical technologies – even when it is realised that expenditure on these technologies accounts for no more than 3–5 per cent of total health care costs, and savings can in any case only be modest. Many countries have introduced some form of regulating system to control the diffusion of costly technology. Some countries have also adopted planning systems to ensure that these technologies are distributed evenly over the population and used in a cost-effective way.

A comparative study of the regulating systems in Europe, conducted under the aegis of the EC, was published in 1988.[74] The analysis showed the wide variation in approach and the widely different effectiveness of the policies adopted.

It is questionable whether regulatory policies and instruments have had any effect on the diffusion of organ transplantation. There can be little doubt that the procedure constitutes an expensive technology: kidney transplants cost US$20–30,000 while heart and liver transplants cost about US$70,000 and $125–200,000 per patient respectively. This is without counting the continuing cost of follow-up and lifelong medication, or that of the specialised infrastructure for organ procurement, testing and transport.

Organ transplantation differs from some other expensive technologies (eg magnetic resonance imaging, linear accelerators for radiotherapy, lithotripsy) in not requiring high capital investment in equipment. Organ transplantation depends on the existence of surgical and medical skills and a combination of specialised facilities including immunology, tissue typing, blood bank, intensive care and isolation units. This means that regulatory mechanisms must

be different from those regulating technologies requiring one large piece of equipment. Table 7.6 presents the different approaches in Europe.

Table 7.6
Regulatory systems for medical technology in Europe

Country, and its approach to regulation
Austria No direct control of medical technologies by the central health authority. Regional health authorities can make their own arrangements. *Organ transplantation* No national planning or approval of transplant centres. Regional authorities are responsible for funding.
Denmark No direct control of medical technology (except drugs) through legislation. Planning and control are through allocation of budgets at regional (county council) level. National Board of Health can designate national centres for highly specialised services. *Organ transplantation* In 1969 the committee on kidney transplantation and dialysis of the National Board designated four centres for KTX; these centres were supported with earmarked financing through the county councils.
Finland Under the National Health System all budgets are annually determined and controlled by the central authority. Local communities are responsible for hospital services, but special services are approved and funded by the government. *Organ transplantation* All transplantations are approved in only one national centre (Helsinki University Hospital) by the National Board of Health.
France The Loi Hospitalière (Hospital Act) 1970 empowers the government to plan hospital facilities according to the national health map (Carte Sanitaire). Purchase of expensive equipment (on a national list) has to be approved by the minister of health, whether in public or private hospitals. Some devices are approved at regional level. The Assistance Publique of Paris plans the diffusion of special services in and around Paris; outside Paris, planning is ineffectual. *Organ transplantation* Regulation of expensive technology does not apply here. France-Transplant can authorise new transplant centres on the basis of quality criteria; no national diffusion plan.
FRG No central planning of technologies; some of the federal Länder have a planning policy (Grossgeräte Planung) but this is indirect, through guidelines and reimbursement contracts with health insurance funds. Technologies used by private doctors are not controlled.

Table 7.6 (continued)

Country, and its approach to regulation

FRG (contd)

Organ transplantation

Not planned by health authorities. Financial arrangements are controlled by KfH (a private institution).

Greece

The 1983 National Health Service Act gives the minister of health power to approve the purchase of equipment. By a 1984 Act a department of biomedical technology was created within the ministry of health to regulate the purchase and use of expensive technologies. Private hospitals are free to buy and use any equipment.

Organ transplantation

Permitted only in public hospitals. The Hellenic Transplant Organisation (YSE) coordinates the transplant services on the basis of the 1983 law. Transplant centres are authorised by the National Health Council.

Ireland

Eight Regional Health Boards come under the control of the central Department of Health. Equipment usually funded through the Department. No national plans for special services, each request for equipment being handled individually on the basis of national needs and priorities.

Organ transplantation

Initially not controlled. After HTX and LTX had been introduced, Dept of Health designated national centres.

Italy

In 1984 the central government issued standards for medical technologies to the regional and local health authorities, who are free to modify these to meet local requirements. The local and regional authorities (USL) authorise the hospitals to buy the equipment; no strict control or planning.

Organ transplantation

Under the transplant law only public hospitals are authorised by the ministry of health to perform organ removal and transplantation. No national planning of transplant centres, but the exchange organisations have made their own arrangements for HTX and LTX at supraregional level.

Luxembourg

Hospital Planning Act 1976 controls the purchase of expensive equipment in public and private hospitals through government authorisation. A list of equipment was published in 1979 and in 1982 a National Hospital Plan listed specialised hospital services.

Organ transplantation

The planning list does not include transplantation.

Table 7.6 (continued)

Country, and its approach to regulation

Netherlands
Government has direct control over expensive health services, not merely equipment, based on legislation (Art. 18 of the Hospital Provisions Act). Reimbursement only if hospital is approved under this Article. Special services are designated on the basis of a National Plan.
Organ transplantation
Kidney transplantation is controlled through Article 18. Heart and liver transplantation are for the moment controlled through research budgets.

Norway
High-technology medical services are allocated to hospitals by the National Board of Health, which is responsible for planning.
Organ transplantation
The National Board has approved one national centre (Rikshospitalet, Oslo) for all transplants.

Portugal
No direct control of medical technology.
Organ transplantation
Transplant centres must be approved by the ministry of health under the revised Transplant Law of 1986.

Spain
No legislative basis for control of medical technology. The autonomous communities are free to determine their policy within their budget. Private hospitals (40 per cent of the total) are not controlled by the Department of Health.
Organ transplantation
Under the Transplant Law of 1979 the central government can authorise both removal and transplantation of organs in public and private hospitals.

Sweden
The Association of Swedish County Councils is responsible for the planning of specialised medical services. The National Board of Health designates the services that are planned on a national basis: the Association of County Councils makes a yearly list of competent candidates from which a choice is made (usually the university hospitals). If a hospital is not on this approved list, procedures are not funded. There is a national policy for the assessment of new technologies.
Organ transplantation
All transplant centres are strictly approved and funded according to this procedure.

Table 7.6 (continued)

Country, and its approach to regulation
Switzerland The central health authority (Federal Offices of Public Health) is limited by the general sovereignty of the cantons. No national planning of health facilities; no legislation to control medical technology. Some cantons control the purchase of equipment in public hospitals. The private sector is not limited in its purchase or use of technology. *Organ transplantation* Although not formally planned, the designation of transplant centres is effective.
Turkey The National Health Service has no planning instrument to control diffusion of medical technology. Hospitals and doctors can make their own plans and attempt to obtain reimbursement from the NHS. *Organ transplantation* Transplant centres are not planned by the NHS, but the National Transplant and Burn Foundation is making an effort to set quality standards. Kidney transplants performed in private hospitals are not controlled in any way.
United Kingdom No specific legislation to regulate purchase and use of medical technologies: regions can decide within their allocated budgets. Department of Health gives general advice on equipment quality and safety. For a new technology, the Standing Medical Advisory Committee chaired by the Chief Medical Officer recommends whether special funds to support its introduction are necessary: these 'pump-priming' funds can be given only to designated national centres. *Organ transplantation* No specific regulation; has to be paid for out of existing budgets. The first KTX centres were given earmarked funds, but this was later left to Regions to determine. Pump-priming funds were allocated to the first two HTX centres, once they had been started with charitable funding.

Of the 18 countries studied, about half have a formalised system to control the purchase and allocation of expensive medical technologies. Only a few (The Netherlands, Belgium, France, Luxembourg) have adopted specific legislation to regulate the use of medical technology, while others (UK, Scandinavian countries) use the health care financing structure, chiefly budget allocation, as a means of controlling the purchase and use of expensive *equipment*. However, such methods do not apply to organ transplantation, as specific equipment does not lie at the heart of this technology; control is at best indirect, through general cost containment in budget allocation. Even where control systems exist, most countries do not apply them to specialised services such as transplantation. The only exceptions are The Netherlands and the Scandinavian countries, which control transplant centres on the basis of a national plan. Some countries (Spain, Portugal, Italy, Greece) do require transplant centres to be approved, but this type of control is generally less effective.

7.5.1 Some case studies of the regulation of technology

The Netherlands

Under the Dutch Hospital Provisions Act, article 18 empowers the Minister of Health to plan specialised expensive services (both equipment and procedures). A national plan is drawn up to allocate these services, and any hospital wishing to provide the service must obtain government approval (a 'certificate of need') – provision of the service *without* prior approval is an economic offence punishable by law. A hospital that has been approved will be reimbursed for the service, and will receive an enhanced budget to enable it to provide the service at the appropriate quality level.

Organ transplantation was allocated under this system in a reasonable geographical spread to seven centres for kidney, two for heart, two for liver and four for bone marrow transplantation.

Belgium

Belgium has a similar law giving the central health authority the power to restrict the purchase and use of expensive medical technologies, but the system applies only to equipment and devices and does not control procedures, which are considered the responsibility of the medical profession; basically, every doctor is allowed to perform any treatment he thinks will benefit his patient. Consequently, any hospital may start a transplant programme if the medical staff consider themselves capable of it. The insurance agencies have contracted to reimburse all procedures performed on patients registered with them. Only if the quality is below standard may the agency withhold payment, or the Chief Medical Officer can intervene.

Recently, a heart transplant service was started in a centre for cardiac surgery (in Aalst) which is without prior experience in transplantation and without immunology facilities. The competition with university transplantation centres which such an initiative represents is intended to have the effect of keeping quality standards high.

Scandinavia

All Scandinavian countries have strict control over the diffusion of transplant centres. Only if the National Board of Health gives approval will the regional health authority (county council) allocate the funds for a transplantation programme. Scandia Transplant has a policy of creating only large transplant centres, to optimise quality and cost effectiveness.

Greece

Since the transplant law of 1984, the Greek National Transplant Organisation (YSE) and the National Health Council have the power to accredit transplant centres, under criteria established by the law. After the introduction of the law, two centres (Athens and Thessaloniki) were authorised and two others were closed.

7.5.2 Conclusion on regulations

In the pioneering period of organ transplantation, it was almost always performed in centres of excellence in surgery and immunology, located in university hospitals. The decision to commence transplantation was taken by leading clinicians, supported by a competent team, the motive being to push back the frontiers of medicine and offer the ultimate in treatment to patients. During this period the role of central and regional health authorities was minimal. Most governments anyway had no instruments for regulation of medical technologies at that time.

This situation prevailed in the 1960s and 1970s, while the number of transplant centres grew slowly because transplantation was still very much an experimental procedure. The picture changed after the introduction of effective immunosuppression around 1980, with diminution of risk and considerable growth in the number of kidney transplant centres. Heart and liver transplant centres also began to proliferate.

This development coincided with an increasing concern on the part of health authorities about the sharply rising cost of health care. This led most countries to explore and introduce more or less stringent measures to contain the cost explosion. The adoption of legislative measures to regulate the purchase and diffusion of expensive technologies was one of these measures. Most of the regulatory instruments were directed against the diffusion of expensive equipment, and were rarely used to control expensive medical procedures – exceptions being the Scandinavian countries and The Netherlands with respect to organ transplants, starting soon after the start of heart and liver transplantation. Other countries exercised a measure of control by requiring authorisation of transplant centres on the basis of minimum quality standards, but not on the basis of a national diffusion plan. The result was often a rapid and unplanned increase in the number of transplant centres, leading to uneven geographic distribution and differences in the size and quality of the transplant services (France, Italy, Spain and Germany).

It was the same situation that led the US National Task Force on Organ Transplantation to recommend in its 1986 report 'that transplant centres be designated by an explicit, formal process using well-defined, published criteria.' Existing centres were to be evaluated against the criteria and only those institutions with the requisite capabilities were to be allowed to perform the procedures. The same concern is now voiced in France, Germany, Italy and Spain, where the number of transplant centres is still growing but many centres perform only a very small number of procedures per year. However, effective measures to check this situation have not yet been taken, with the exception of France where proposals for restricting the number of transplant centres were accepted in the summer of 1990.

7.6 ROLE OF FINANCING (HEALTH INSURANCE) AGENCIES

7.6.1 Financing systems and organ transplantation in the USA

When organ transplantation was first developed in laboratories and clinics in the USA and Western Europe during the 1950s and 1960s, the financing of these procedures was not considered a real problem. As long as the transplants were considered to be 'experimental', costs were usually covered by research funds, university grants or sometimes charitable funds. The costs were borne by the hospital institution and no demands were made on the patients or the health care financing agencies. Consequently these financing agencies were not really concerned, also because the transplantation was still quite insignificant in volume. However, as organ transplantation began to move beyond research, the method of financing these expensive procedures became increasingly important. The following example may clarify this development. Until the early 1970s, treatment for 'end stage renal disease' (dialysis and kidney transplantation) was not reimbursed in the USA under the federal insurance scheme. Thus, only people with good private insurance or those who could pay out of their own pocket had access to this life-saving treatment.

Faced with this criticism and the demand for access, the federal health agency decided in 1972 to cover ESRD (dialysis and transplantation) fully under the Medicare/Medicaid scheme. At that time the federal financing agency (now Health Care Financing Administration – HCFA) made a calculation of the total costs involved in this decision. In 1974 this was calculated at US $242 million, covering dialysis and transplants. By 1983 this had increased to US $2.1 billion (including US $250 million for kidney transplants only). There was serious concern by that time on the part of politicians and financial experts that the State could not afford this. However, HCFA did not consider any cuts in the programme since it had been proved in several studies (requested by the HCFA) that kidney transplantation was more cost-effective in the long run than dialysis, and provided better quality of life to the patient. Today there is no doubt on any side that kidney transplants are worth the money and both public and private insurances are willing to cover all costs.

With the introduction of heart and liver transplantation things went somewhat differently. During the first 10 years of their development these procedures were considered to be 'experimental' or 'not yet established' by the federal financing agencies and consequently no procedures were covered under Medicare/Medicaid programmes. Only a few private insurance companies were willing to pay for these transplants. At the time the number of these transplants was still relatively small. However, this changed at the beginning of the 1980s when these technologies matured. Pleas from individual patients for financial help in the press and on television were becoming commonplace. Most financing agencies held off and persisted in calling transplants 'experimental'. HCFA foresaw a considerable demand for heart and liver transplantation, especially after the introduction of cyclosporin A (approved in 1983 by the Food and Drug Administration, FDA). The federal

financing agency wanted to be prepared and requested a cost benefit analysis. That study (R W Evans, Battelle Human Affairs Research Centers) became available in 1984. On the basis of its findings provisions were made in the 1986 Omnibus Budget Reconciliation Act (OBRA) for the coverage of heart and liver transplants under the federal health care schemes. Most of the United States have now followed these recommendations. (The exception is the State of Oregon, where health care policy makers decided in 1987 to curtail funding for organ transplantation almost completely, albeit with considerable public outcry.) The recommendations are that extra-renal transplants are to be reimbursed only to hospitals that have proved their ability to run a successful transplant programme. Criteria for this evaluation have been established.

The picture that results from these US examples is that organ transplantation developed without much interference from the health care financing agencies until the moment that the technology was considered a mature, established health service. From that moment on, financing agencies played a critical role, sometimes delaying the diffusion of the technology by withholding reimbursement. In the following paragraphs we will analyse the corresponding developments in Europe.

7.6.2 Financing systems and organ transplantation in Europe

In an earlier chapter we described and analysed the two dominant types of health care system found in Europe: the national health care system, run by the central government and financed out of general taxation and the social security insurance system, in which both public and private insurance agencies contract services from hospitals and doctors and negotiate reimbursement fees. Social insurance is mandatory and premiums are paid out of wages. The role of the central government differs from country to country. In both these systems there exists the fundamental rule that those insured have a right of access to every kind of medical treatment prescribed by a doctor, without consideration of the cost. It is the responsibility of the doctor to provide only treatment that can be considered 'effective' and 'appropriate' for the patient. In some countries the rights of patients go as far as to include transplants abroad, if the national health service cannot provide this.

In a public or national health care system, the money to provide the care is allocated from the central tax fund to the regions (on the basis of demographic and epidemiological data) and to the different care institutions in that area. These institutions have a fixed yearly budget from which to finance all the care provided to their clients. There is almost complete freedom for the doctor or hospital to provide expensive services, but the budget limits the volume.

In a social insurance system the situation is basically the same: through their insurance all clients have unlimited right to medical care, whatever the cost of treatment. Insurance agencies must reimburse whatever treatment a doctor prescribes and provides. Therefore the system is open-ended, but for two important limiting factors. One is that insurance agencies can influence the volume of care by setting lower reimbursement fees to discourage

doctor prescribes and provides. Therefore the system is open-ended, but for two important limiting factors. One is that insurance agencies can influence the volume of care by setting lower reimbursement fees to discourage provision of service. Another instrument used by insurance agencies is to exclude some (new) treatments from the insurance benefit package until it is proven that they are appropriate and cost effective. This, however, is not possible in all countries, since the benefit package is not always clearly defined.

Transplantation costs

It is well known that the 'real' costs of transplantation differ quite considerably from the amounts that are reimbursed to the hospitals by the insurance agencies. There has been ample discussion of what should be included in a true calculation, but there seems to be consensus on the following items:
- pre-transplant costs (laboratory tests, transfusions)
- the transplant operation
- hospital stay
- drugs (immunosuppression, antibiotics)
- blood and blood products
- outpatient visits in the first year
- immunosuppressive medication in the first year.

These items represent the direct costs of transplantation; but added to this should be:
- organ removal (donor operation, organ preservation and transport)
- tissue typing and matching
- medication and outpatient visits after first year.

Finally, if one wants to calculate the true costs of a transplant programme, one should also add the costs of the hospital infrastructure, of organ procurement and training of personnel. The following average costs for transplants (total cost for first year) have been reported in three countries:

Transplant	UK	Sweden	USA
Kidney	£ 8,000	Skr 150,000	$ 35,000
Heart	16,300	300,000	75,000 (±18,000)
Liver	25,000	600,000	178,000 (±67,000)

In The Netherlands several cost calculations have been made concerning organ transplants. In these studies not only the direct cost of transplants have been calculated, but also what has become known as the 'programme cost', that is the integral cost of a transplant (for the first year) in a programme with a fixed number of transplants. The following costs result from this approach: If one looks at the problems surrounding the financing of organ transplants from the time of introduction, a certain pattern arises. In the first phase of development, transplants were usually considered as 'experimental' and

Programme costs of organ transplants in The Netherlands

Transplant	Operation only	Programme costs	Follow-up
Kidney	Dfl 22,000	Dfl 69,000 at 400 Tx per year	Dfl 6,000 per year
Heart	Dfl 23,000	Dfl 175,000 at 60 Tx per year	Dfl 28,000 per year
Liver	Dfl 40,000	Dfl 250,000 at 30 Tx per year	Dfl 28,000 per year

Sources: Health Council of The Netherlands 1988, Institute for Medical Technology Assessment, Rotterdam 1988

consequently financed from research funds. Once the technology had matured and transplant programmes started to grow some problems arose: it became necessary for (new) transplant centres to create new facilities and employ more personnel. In most countries the financing agencies (national health authorities or insurance agencies) made no difficulties over paying for these transplants, although the amount of money included in the budget or the reimbursement fee was not sufficient to cover the real cost. In several countries this situation threatened to block the diffusion of transplants. Several solutions have been found to resolve the problem:

- in some countries (the UK, Scandinavia, Italy and The Netherlands) the central health authority defined transplants as 'special, supra-regional services' and supplemented the budgets of approved transplant centres
- in other cases (Germany, UK, Turkey) these extra costs were borne by charitable funds
- in one case the cost of heart and liver transplants, including the necessary infrastructure, was financed completely from research grants (The Netherlands).

A second problem in financing transplants concerned the cost of organ removal, both in a general sense (who pays for operating an organ procurement and exchange programme?) and in a narrow sense (who pays for the removal of organs from an individual donor?).

The first issue has been solved by the central health authorities taking over the funding of procurement and of exchange organisations that started as private initiatives (ScandiaTransplant, UK Transplant Service, Swiss Transplant, and France-Transplant). In other countries the organ procurement and exchange agencies were financed from the start by the Ministries of Health (Spain, Portugal, Greece, Italy). Eurotransplant is now the only organ exchange organisation that is not financially supported by the government; its services are paid for by the recipients' insurance agency. The second issue (who pays for the removal of donor organs?) has in a number of countries (especially those with a social security insurance system) been a stumbling-block in the development of organ transplantation. On the basis of their

contract with the patient, insurance agencies do not cover any medical procedures after death. This meant that the cost of the removal of organs (nephrectomy) had to be paid by the hospital or worse, by the family of the donor. In the 1960s and early 1970s the removal costs were paid in a number of countries by charitable funds (Kidney Foundation, Dialysis Patients' Association); but when the kidney transplant programmes started to expand in the 1970s it became customary to let the donor costs be reimbursed by the insurance agency of the recipient. This is now standard practice in all social insurance health systems as well as private insurance systems. However, not all problems were resolved in this way. The costs of the donor operation have increased over the years, especially with multi-organ donation; the result is that in a number of countries the reimbursement fee to the donor hospital does not cover the true cost of the procedure, so that some hospitals have become reluctant to remove organs. In most countries negotiations are now taking place to increase the reimbursement fees for multi-organ donor operations. In some countries financial incentives have even been created to induce (non-transplanting) hospitals to be active in organ procurement (eg a bonus system for intensive care wards).

7.6.3 Some case reports

Denmark

Kidney transplantation was introduced into Denmark in 1963. Early in the diffusion of the technology the Danish health authorities recognised the cost-saving potential of this procedure in relation to dialysis and when the National Board of Health designated national transplant centres in 1968, these centres received an extra budget to cover the initial infrastructural costs. Also, the Nordic Council of Ministers gave a grant to Scandia Transplant in 1969 to get organ procurement and exchange off the ground. As a result Denmark already had 28 kidney transplants per million population in 1977 – five times the average for western Europe! When around 1980 there was a stagnation in organ procurement, the National Board of Health again gave a financial impulse, resulting in a further rise of the number of kidney transplants in 1984–7.

Around 1984, when the introduction of heart and liver transplantation was considered feasible in Danish transplant centres, the National Board of Health requested an evaluation of the technical, financial and social implications. This study was based on US and UK data. The main conclusion was that heart and liver transplants were medically and financially worthwhile and could be performed in Denmark. It was proposed that the extra cost for these procedures would be covered by the regional budgets, supplemented by a state grant to the transplant hospitals. However, it was not until 1990 that heart and liver transplants were performed in Denmark. This delay was due to the intense debate over the acceptance of brain-death criteria and not for financial reasons. In fact, under the Danish national health system every citizen is entitled to treatment abroad if the national hospitals cannot provide this service and indeed since 1983 the Danish health authorities have paid for

Danish patients to have heart and liver transplants outside Denmark (in The Netherlands and Germany, among others).

Ireland

In Ireland heart and liver transplantation started in 1985 on the initiative of the transplant centres: the cost had to be paid from the existing budgets. Even when the health authorities intervened and designated national transplant centres, no additional funding was provided. It was reasoned that heart transplantation had to be paid out of the budget for cardiac surgery. As a result, heart and liver transplant programmes have a shaky financial basis and have not developed satisfactorily.

The Netherlands

In The Netherlands the introduction of heart and liver transplantation around 1984 has been the cause of a debate on 'the limits of medical care'. For the first time the National Sick Fund Council exercised its power to refuse to admit a new technology to the social insurance benefit package until its (cost) effectiveness had been proven, whereas in the past new procedures had been included routinely whenever the medical profession considered them useful. Heart and liver transplants were considered to be 'experimental procedures under evaluation', and the Sick Fund Council provided a grant to perform a technology assessment. The grant included not only the cost of the assessment but the full cost of a programme of 30 transplants a year. In this way, the funding of assessment studies was used as a mechanism for controlling the diffusion of new technologies. Recently (1990) the decision has been taken to finance heart transplants under the regular social insurance system, while liver transplants are still under evaluation.

The diffusion of transplants in The Netherlands has been influenced negatively, to some extent, by problems over the financing of organ removals. Since hospital budgets were introduced in 1984, the hospital administrators have been directly confronted with the fact that the standard reimbursement fee for organ removal does not cover the full cost of nephrectomies and multi-organ procedures. The insurance agencies have so far been unwilling to negotiate higher fees. Since 1989 the Dutch Kidney Foundation has stepped in and supplements the existing fees to the hospital, hoping that this will work as a political lever to speed up the negotiations.

Catalonia

The health authorities of the Spanish autonomous province of Catalonia have approached the problem of organ shortage in a direct way, using financing as a positive control. All donor hospitals – public as well as private – are paid a fixed sum (forfait) for every donor that is maintained in the IC unit. All transplant centres get an extra yearly allowance plus a financial 'bonus' for every transplant that is performed. This is not a personal allowance but a grant to the transplant unit, to be spent on scientific work, literature or visiting a congress.

7.6.4 Conclusions

Thus, financing agencies have had a less than major, sometimes marginal influence on the diffusion of organ transplantation in Europe. In almost all countries (except for The Netherlands and Turkey) organ transplants have been financed from the start on a regular basis: either directly from the national health budget or under the social insurance reimbursement scheme. In most health care systems citizens are entitled to all kinds of medical treatment, without exception, and financing agencies are not in a position to curtail this right by excluding certain procedures (such as transplants).

In some countries, early diffusion has been positively influenced by the financing agencies or, in some cases, charitable funds which the funds made available to create the necessary infrastructure in the transplant centres. The later diffusion of organ transplantation has been accelerated, in a number of countries, by financing agencies introducing financial incentives to overcome the shortage of donor organs.

In general, financing agencies in European countries, unlike their American counterparts (HCFA, Blue Cross, Blue Shield), have not been very active in evaluating the economic aspects of organ transplantation and few have used existing information to support their policies.

7.7 ROLE OF THE PUBLIC AND THE MEDIA

There is no *official* role for the public (as potential consumers of medical care) or for the media in decision-making over the introduction of new medical technologies. However, it would be a mistake to brush them aside as unimportant or to under-estimate the influence that these groups can have on the course of events. We have only to recall the cases of Jamie Fisk (1982 paediatric liver transplant) and Baby Jesse (1986 paediatric heart transplant) in the USA to realise that consumer pressure groups or even individual patients have successfully forced the hand of health authorities when it comes to admitting new medical technology such as organ transplantation or paying for it.

The media (television and press) have sometimes had a profound influence, both positive and negative, on the manner in which transplantation developed, as can be documented in a number of countries. Often there has been intense interaction between the public and the media, which makes it difficult to tell which was the more decisive. For instance, public pressure groups have used the media to promote their cause with the government or other decision-making bodies, while the media have sometimes taken the initiative by presenting (often sensational) news items on transplantation, and the public has reacted to that in different ways.

7.7.1 The role of the public

It is hardly possible to give a complete overview of the many different ways in which the public (acting as individuals or as groups) have concerned themselves with the issues of organ donation and transplantation and have

tried to influence the course of events in their countries. However, we can group these activities into some broad categories:

a) The promotion of organ donation

In almost all European countries the public is actively involved in the promotion of organ donation. In most cases it is the patients' associations (eg kidney and heart foundations) who take the initiative and support and fund public campaigns. In the UK and The Netherlands these foundations organise public opinion polls to evaluate the effects of their efforts over time. Some individuals have played an important role in influencing public opinion: for example in Greece George Kastrinakis, a well-known journalist waiting for a second kidney transplant, has written a book about his situation and gives public lectures on the problems of organ shortage. Individuals in positions of official authority have also been influential in promoting organ donation: the best example is Pope John Paul II, who has declared before an audience of medical specialists in the Italian town of Bari that organ donation is 'a gift of life' and 'an act of supreme charity' in keeping with the Christian ethic. Other religious leaders have expressed similar views.

b) The public as a political pressure group

In a number of countries the public has acted as a pressure group to influence decision making concerning the introduction of heart and liver transplantation. In Sweden, Denmark and The Netherlands patients have combined forces (often together with doctors having an interest in transplantation in the background!) to put political pressure on the health care authorities. They wanted them to allow patients going abroad to receive a transplant and have this paid for under the regular insurance scheme. In many cases politicians have been approached and found willing to ask provocative questions in parliament about the slowness of the decision-making or the delaying tactics of the health authorities. In The Netherlands, patients' associations and other groups from the public protested against the policy of heart transplant centres to use age limits in patient-selection, and have used the political lobby with some success.

c) Funding of transplant facilities

In Germany and The Netherlands patients' associations have raised funds to support the diffusion of transplantation. The German Kuratorium für Heim-dialyse (Association for Home Dialysis) supplies the funds for extra personnel and infrastructure in transplant centres. In The Netherlands the Kidney Foundation and the Heart Foundation have paid the salaries of regional transplant coordinators and are now supplementing the reimbursement fee for multi-organ donor operations. In the UK the first heart transplant programme in Papworth was supported from charitable funds, until finally the Ministry of Health decided to put money into an assessment study and pay for the transplant programme.

d) Patient-support groups

In several countries transplanted patients have formed support groups or networks to help potential recipients waiting for a heart or liver. The Dutch group of heart transplant recipients Harten Twee (Two of Hearts) gave legal, financial and social support to the patients during the period when heart transplants were not officially funded. This group also arranged an 'air-bridge' to heart transplant centres in the UK and the USA.

e) The transplanted patient as 'success story'

Early on in heart and liver transplantation, long-term survivors acted as 'living proof' of the benefits of transplantation. In the UK one of the first heart transplant recipients in the Papworth programme, Mr Keith Castle, appeared many times on television and even in medical conferences giving testimony of 'what good a heart transplant can do for you'.

f) Dissenting groups

Not all parties from the public have been in favour of organ donation and transplantation. Sometimes the opposition even came from within the medical profession: in the UK some doctors have refused to participate in heart and liver transplant programmes because they had doubts about the brain-death criteria. Other NHS consultants have voiced their resistance to the diffusion of transplantation because they feared it would drain away too much of the meagre resources of the Health Service. In Denmark there was initial opposition from the cardiac surgeons who said that the priority should be with the expansion of the cardiac bypass programme and not with starting heart and liver transplantation.There is opposition to organ donation and transplantation from some minority religious groups, especially orthodox Jews, fundamentalist Muslims and traditionalist Christian movements. However, this concerns personal choice and attitude and has not led to any public protest against transplantation.

Conclusions

It is not possible to determine to what extent the public, groups or individuals, have actually influenced decisions concerning organ transplants in different countries. There are no reports documenting that public pressure groups have successfully blocked the introduction and diffusion of organ transplantation in any European country for a sizeable period, with the exception of Denmark (where a nation-wide public debate on brain death led by the Ethical Council has postponed the start of heart and liver transplantation for several years). On the other hand, there is ample evidence that public initiatives and appeals to the politicians and health authorities have set in motion the slow wheels of bureaucracy and speeded up the decision-making process.

7.7.2 The influence of the media

The media have been involved with the topic of organ donation and transplantation in many different ways, influencing the process of diffusion in both a positive and a negative sense. Again we have summarised the manifold observations from different European countries in some broad issues:

a) Official education campaigns

The media (mostly television) have participated in official campaigns initiated by the health authorities to inform the public about new legislation on organ donation and transplantation. In Belgium, Greece, Denmark and Sweden health authorities have informed the general public through the media of the consequences of the new law. At the same time information was given on many technical aspects of donation and transplantation as well as on the brain-death concept. In Greece the recent public campaign to combat the shortage of donor organs used television to approach selected target groups such as secondary schools and the army in an effort to promote participation in a donor card scheme.

b) Popular scientific journalism

Media (television, magazines and newspapers) in a number of countries have featured regular programmes and articles on new developments in medicine, including organ transplantation. These are 'serious' attempts at scientific journalism, aiming to give a balanced view on both the benefits and problems of new technologies. In the UK the BBC broadcast a seven-part documentary on the heart transplant programme in Harefield in 1982, featuring debates with proponents as well opponents from the medical field. Dutch television has broadcast a series on new medical technology: one of them a prize-winning documentary on liver transplantation, focusing on difficult ethical issues. In Ireland and Denmark, television programmes on organ transplantation have featured 'foreign experts' who commented on the benefits of heart and liver transplantation, at a time when the health authorities had not yet decided to introduce or fund these procedures.

c) 'Sensational' journalism

Far more common than the efforts at scientific journalism have been the media reports on sensation or scandal in transplantation medicine. In many countries there has been a high-profile media interest in the 'heroic' side of heart and liver transplantation, in the excesses such as commercialism in organ donation and in the personal plight of recipients on the waiting list or of bereaved donor families. Sometimes the effect of these news items has been detrimental to the attitude and actions of the general public, as is reported from the UK, The Netherlands, Italy, Spain and Turkey. In these countries the number of organ donations dropped dramatically directly after broadcasts or reports on the abuse of potential donors, doubtful brain-death criteria or doctors making fortunes by selling donor kidneys.

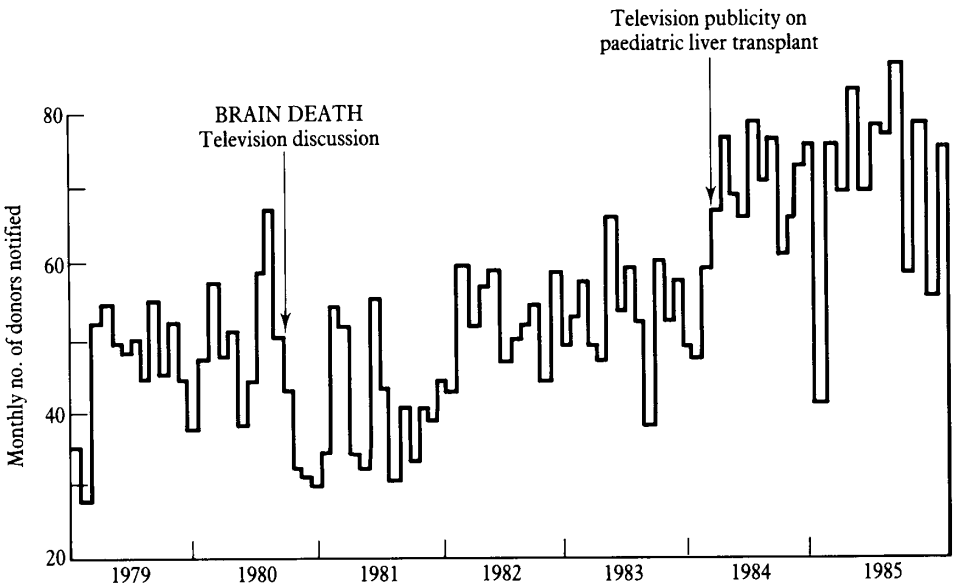
d) Public campaigning

In some cases the media have been the platform for different pressure groups and interested parties in organ transplantation to bring their message to the general public. There are a few examples of patients waiting for a transplant who have made a direct appeal to the public for a donor organ or for financial support (UK, Italy). Local and national television stations may be involved in the promotion of donor card schemes (Greece, UK, Netherlands) or where the kidney patient associations have started 'public awareness' campaign. In The Netherlands the Dutch Kidney Foundation has recently started to approach the public through advertising in newspapers and on television.

Case-report on the United Kingdom

The power of the media to influence the attitude of the public towards organ transplantation, and as a result the process of diffusion of the technology, is nowhere better illustrated than in the UK. The first example involves the brain-death criterion: in 1979 the medical Royal Colleges published a memorandum on 'The diagnosis of death' in *The Lancet* and the *British Medical Journal*, describing and explaining the brain-death criterion and the methods of diagnosing brain death. The Ministry of Health thereupon issued a handbook, describing a code of practice for organ removal from brain-dead, artificially ventilated donors. This was challenged on technical and moral grounds by a small group of doctors, one of them being a cardiologist from the heart transplant centre in Papworth. In October 1980 the BBC television service transmitted a 'prime-time' programme in which the practice of determining brain-death in England was viciously attacked (under the title: 'Transplants – are the donors really dead?). The programme was an uncritical

Figure 7.2
Donors notified of UK transplant service (monthly totals)



presentation of half-truths and false accusations, in which Dr Evans, the protesting cardiologist, played a leading role. There was an immediate dramatic fall in the number of kidney donors which seriously affected the renal transplant programme nationwide, as is shown in Figure 7.2.

This Figure also shows that television broadcasts can have a positive effect on donation: in 1983 the BBC featured a news broadcast in which they presented the story of a paediatric liver patient who was urgently waiting for a donor organ. Not only was a paediatric donor liver offered within days, but there was also a general rise in donation from the public, an effect lasting several months.

Conclusions

The different examples of the role of the media in reporting developments in organ transplantation show that the potential influence of the media should not be underestimated. Transplantation medicine, especially when there is a persistent shortage of donor organs (as there is almost everywhere) relies very much on public approval, and examples such as the UK show that the public is highly susceptible to media influence. Especially television has proved to be a most powerful medium when it features emotionally charged issues such as transplantation and organ donation. It is obvious that this calls for careful, responsible journalism.

In few European countries have the effects of the media on the diffusion of transplantation been as extreme as in the UK: in Scandinavia (except Denmark), Belgium, France, Greece, Ireland and Portugal the media have generally reported in a positive, supportive way on organ transplantation. Little interest from the media has been observed in Germany, Switzerland or Luxembourg. Negative influence from the media was reported from Italy, Spain, The Netherlands and the UK.

7.8 TWO CRUCIAL FACTORS IN THE DIFFUSION OF TRANSPLANTATION

Several decisive factors in the process of acceptance and diffusion of organ transplantation have already been described. They include the existence, in the country concerned, of

- medical centres of excellence,
- medical professionals with an innovative attitude to clinical medicine and research,
- an organisational infrastructure for organ procurement and exchange, and
- legal and financial arrangements that support organ removal.

In this section we focus on two other important aspects: the acceptance of the brain-death criterion, an issue that has provoked heated discussions among the medical profession, but in some countries also amongst the lay public; and restriction of the number of transplant centres, on the basis of the belief in a positive relation between a high volume of transplants and their quality and outcome.

7.8.1 The brain-death criterion

The concept of brain death (that is: the irreversible cessation of all functions of the brain) was described in Paris as early as 1959. However, at that time it was only of interest to neurosurgeons and neurologists theorising on the functioning of the brain. The notion of the clinical importance of brain death came in the 1960s, when increasing numbers of patients were being treated in intensive care units, mechanically supported on ventilators. In that situation it became all-important to be able to diagnose death in a patient, in order to know whether further medical treatment and support was of any use (and even ethically acceptable).

In 1968 the Medical School of Harvard University published its 'criteria for diagnosing brain death' and gave practical guidelines for clinical and technical examination. A number of US states then passed brain-death laws based on these criteria. However, in 1971 the Medical School of the University of Minnesota produced another version of the brain-death criteria, claiming that brain death could be determined on the basis of clinical diagnosis alone and that supplementary technical tests (such as the EEG advised by Harvard) were unnecessary. In most European countries brain death has since 1970 come to be accepted as equivalent to death, but different approaches from the use of clinical and technical tests have been developed.

Some countries accept brain death on the basis of repeated clinical examination only, and supplementary technical tests are not required (UK, Portugal). Most countries follow the French approach, in which one or two EEGs are required (France, Belgium, Luxembourg, Finland, Greece, Netherlands, Italy, Ireland, Turkey). Finally, there is a group of countries where the code of practice states that a cerebral angiogram to confirm cessation of brain functioning is desirable or mandatory (Germany, Austria, Norway, Sweden, Spain, Switzerland). Until recently, the only country in Europe that did not accept the brain-death criterion in its current definition – irreversible cessation of all brain(stem) function – was Denmark. Consequently no removal of donor organs from ventilated brain-dead patients could take place there, and heart and liver transplantation were not allowed in Denmark. In 1989 an attempt was made by the Danish Council of Medical Ethics to solve this problem by proposing a definition in which brain-death and cardiac death were combined. This, however, was at best a political solution to mollify the transplant surgeons who wanted to start heart and liver transplantation. Finally in 1990 the Danish parliament passed new legislation in which brain death was accepted as the legal criterion for determining death.

It is important to emphasise that medical professionals in most countries accepted the brain-death criterion without much discussion in its relation to the problem of determining death in ventilated patients in the ICU. When, inevitably, brain death became connected with organ removal from mechanically ventilated patients for transplantation, this led to fierce debate on the ethical and legal aspects of brain death. This discussion, which involved not only the medical world but in some cases also the lay public, has certainly influenced the diffusion of organ transplantation, especially heart and liver transplantation.

As a result of the controversy, a number of countries have included the definition of brain death in their transplantation legislation, sometimes also giving detailed requirements for diagnosis. Others merely require the doctor to determine death according to a national medical code of practice.

In Europe the current situation is the following:

Countries that accept brain-death medically and legally:
Austria, Finland, France, Greece, Italy, Luxembourg, Norway, Portugal, Spain, Sweden and Denmark (after June 1990)

Countries that accept brain-death medically only:
Belgium, Germany, Ireland, Netherlands, UK, Switzerland, Turkey

Countries that did not accept brain-death:
Denmark (before June 1990).

7.8.2 The quality and number of transplant centres

In medicine the well-known adage that 'practice makes perfect' has particular relevance. It has repeatedly been demonstrated that doctors who perform a procedure frequently usually have significantly better results than those who treat only a small number of cases. Several American studies have shown that this is particularly true in surgery, in relation to operative mortality and post-operative morbidity. This phenomenon has not been studied recently for organ transplantation, but there is every reason to believe that it holds true there. Organ-exchange agencies, which have a good overview of the situation in their area, often remark that centres with larger numbers of transplants per year have consistently better outcomes than smaller centres in comparable groups of patients, although there are no methodologically sound studies available to document this.

The argument had little meaning during the initial period of organ transplantation, when the transplant procedure itself was developing and numbers of transplants were small. Even today, it is well known that all new centres go through a learning phase and that the results improve over time. But now that most national transplant programmes have reached a stable phase, it would seem logical to try to maximise or optimise the number of transplants per year per centre. This is surely possible only when the number of centres itself is controlled in some way.

The issue of the optimum volume per centre, and the maximum number of centres in a country, has been raised repeatedly in transplant circles. However, it is not a popular subject since it sets large established centres and small new centres against each other. Consequently, there is little consensus nowadays on the optimum size of transplant centres.

Recently the federal health financing agency in the USA (HCFA) has formulated some general criteria (not based on scientific data of transplant outcomes) to determine the minimum size of kidney, heart and liver transplant centres. These criteria (based on the annual number of transplants and the number of years of experience) are now used to determine whether transplant centres qualify for reimbursement through the Medicare programme. It is

remarkable that of the 131 heart transplant centres in 1988, only 22 have been approved by HCFA. A similar situation obtains for liver transplantation. This is in sharp contrast to the policy of UNOS (the US National Organ Sharing Network), which has accredited all 131 heart transplant centres for participation in organ exchange and transplantation on the basis of the professional qualifications of the teams. However, UNOS does not look at volumes or outcomes. This controversy has led to discussions in American transplant circles and in Congress, where some have suggested that the number of transplant centres should be controlled more strictly. However, neither the Reagan nor Bush administrations have been in favour of this and little has changed so far.

This issue of volume and quality has also been raised in Europe, where individual countries have different policies in health care planning and regulation. This question is especially relevant today, when the growth of transplant programmes is limited by the shortage of donor organs. The larger centres now see their future endangered as new small centres emerge but the number of organs stays the same. If we look back at Tables 6.10, 6.13 and 6.15 (Chapter 6), we observe that the diffusion of transplant centres varies in the different countries. The average number of transplants per centre also seems to vary widely. To get a better insight in this we will now examine these data in more detail.

In Table 7.7 we show the diffusion of kidney transplant centres in a number of countries (with an established transplant programme), looking at the volume of transplants per centre. We have taken 50 kidney transplants per centre per year as the minimum requirement in terms of quality and efficiency.

Table 7.7
Size of kidney transplant programmes in 1988

		Volume per year		
Country	No. of centres	0–50	over 50	maximum
W. Germany	28	13	15	189
France	41	24	17	120
Belgium	7	4	3	122
UK	34	20	14	100
Italy	24	22	2	83
Netherlands	7	1	6	91
Sweden	4	0	4	132

These data show that, in the countries here presented, planning leading to concentration of transplants in a limited number of centres has taken place only in Sweden and The Netherlands: almost all centres in these countries perform more than 50 kidney transplants a year. In Germany, Belgium, France and the UK only about half of the centres perform 50 kidney transplants or more. In Italy the situation is extreme: only two out of 24 centres perform 50 transplants a year, while many do fewer than 10. In Table 7.8 we present

similar data for heart and liver transplantation in these countries. In this case we have taken 20 transplants as the minimum volume per centre per year.

Table 7.8
Size of heart and liver transplant programmes in 1988

Country	No. of centres		Volume per year 0–20	over 20	maximum
Germany	HTX	15	11	4	93
	LTX	13	9	3	104
France	HTX	33	22	11	118
	LTX	26	20	6	74
Belgium	HTX	5	2	3	41
	LTX	4	3	1	113
UK	HTX	5	2	3	139
	LTX	5	3	2	113
Italy	HTX	9	5	4	46
	LTX	6	5	1	27
Netherlands	HTX	2	1	1	32
	LTX	2	2	0	17
Sweden	HTX	3	2	1	27
	LTX	3	1	2	22

Again we see almost no concentration or planning in Germany or France: in these countries almost 60 per cent of all heart and liver transplant centres perform fewer than 20 transplants a year. In Italy, heart and liver transplantation is more concentrated than for kidneys although the number of transplants per centre is still small, as programmes have started rather recently. In the UK, Belgium, The Netherlands and Sweden there is more evidence of concentration and planning. It is striking that in countries that started heart and liver transplantation early (France, FRG, UK, Belgium) the field is dominated by a few very large centres, doing 100 transplants or more a year – these being the centres which pioneered the technique – whereas the *average* transplant centre in these countries has a much smaller workload.

The fact that the number of transplant centres is growing faster than the volume per centre has given cause for concern in some countries. In Germany and Italy the medical associations of transplant doctors are discussing measures to restrict the start-up of new centres. In France the government is now regulating the formation of new centres. A recent law (24.9.90) states that all transplant centres must be approved by the government. The approval will depend on an evaluation of the experience and results of the centres. Recently the government has issued a national plan, giving the following maximum numbers:

Transplant type	Centres in 1990	Approved maximum
Kidney	46	39
Heart	36	29
Liver	29	24

It is not yet clear how the proposed reduction in the number of centres will be brought about.

7.9 ROLE OF ASSESSMENT STUDIES

Studies on the effectiveness of emerging medical technologies have become quite abundant in recent years. Most medical journals now contain articles on the cost-benefit, cost-effectiveness and quality-of-life analyses of medical procedures. In some countries institutes have been established which dedicate themselves to the task of medical technology assessment, as it has become known: the Office for Health Technology Assessment (OHTA) in the USA, the Centre d'Evaluation de la Diffusion des Innovations Technologiques (CEDIT) in France and the Institute of Medical Technology Assessment (IMTA) in The Netherlands, to name but a few.

However, the crucial question remains: do these technology assessment really influence decision-making by health authorities and politicians? Or is medical technology assessment for the time being only of interest to academics? Looking at the (rather short) history of assessment studies in medical technology, one is inclined to say that the latter situation prevails. Often, the study has been done at a time in the development of the technology when the outcome can no longer have a major impact on the pattern of diffusion, for instance with the CT scanner. In other cases, where evaluation results have been available before diffusion took place in these countries, the outcomes have not influenced the decision-making, because other interests (eg of a national industry) predominated, as in the case of the lithotripter and magnetic resonance imaging. Much depends on how the results of MTA studies are presented and to whom.

7.9.1 Technology assessments of organ transplantation

Table 7.9 gives an overview of the studies that have been conducted in Europe and the USA.

Table 7.9
Assessment studies on organ transplantation: Europe and the USA

Country	Assessment study
USA	1983 NIH Consensus Conference on liver transplantation (cost-benefit analysis); 1984 National Heart Transplantation Study by the Battelle Institute (cost-effectiveness study); 1990 Assessment of liver transplantation by OHTA *Effect of the study* All studies were done at the request of the federal financing agency (Medicare, HCFA), to aid decision-making on reimbursement policies. The first two studies were decisive in influencing the decision to reimburse HTX and LTX as a 'regular health service, for selective indications'. These studies also had major effect on the decisions of transplant teams in Europe to start HTX and LTX and influenced the attitudes of decision-makers there.

(*contd*)

Table 7.6 (continued)

Country	Assessment study
Denmark	1985 Study on the introduction of heart and liver transplantation, commissioned by the National Board of Health (feasibility study and economic evaluation). *Effect of the study* This study was done prior to the introduction of HTX and LTX in Denmark. No decision was taken following this study, because the debate on brain-death was unresolved. In 1989 the Institute of Social Medicine at Odense did a revised study to calculate the actual need for organ transplants in Denmark.
Sweden	1987 Study commissioned by the National Board of Health and Welfare on the need for organ transplants in Sweden (cost-effectiveness study). *Effect of the study* Although the study was completed after HTX and LTX had been introduced in Sweden, this study was the basis for political decisions on the national planning of transplant centres in Sweden, which has now been effected.
Netherlands	1986 Study on kidney transplants and dialysis by the Health Council; 1984/88 Studies by the Health Council on heart transplants, liver transplants, pancreas transplants and bone-marrow transplants; 1988 Studies by the Institute for Medical Technology Assessment (commissioned by the National Sickness Fund Council) on heart and liver transplantation. *Effect of the study* All these studies affected the decision-making of the Ministry of Health on the planning of transplant facilities, and of the Sickness Fund Council on the financing of transplants in The Netherlands. Heart transplants and bone-marrow transplants have recently been admitted to the insurance benefit package, liver and pancreas transplants are still considered 'clinical experiments' and funded by research grants. The studies by the Institute of Medical Technology Assessment (IMTA) were 'full-scale' MTA studies, including cost-effectiveness and quality-of-life aspects.
UK	1982/1985: study on heart transplantation by a team of Brunel and Cambridge Universities, commissioned by the Department of Health. *Effect of the study* The project was a comparative study of the HTX programmes at Papworth and Harefield hospitals, examining cost-effectiveness and quality of life. The immediate effect was that the Department of Health decided to fund HTX in these centres as a NHS service, and no longer as 'clinical research'. There was no clear influence on NHS policy to start and fund other HTX centres.

(*contd*)

Table 7.6 (continued)

Country	Assessment study
Ireland	1985/86: study by the Department of Health on the requirements for liver transplants in Ireland (feasibility study). *Effect of the study* The report was mainly based on the observations and judgements of a hepatologist, who was brought over from the UK as an expert. On the basis of this study a national LTX programme was started in one centre in Dublin (and a second LTX centre was closed down.)
Italy	1988: study on the coordination of transplant services in Italy by the heads of the larger transplant centres (in Milan). *Effect of the study* This was a feasibility study undertaken to reorganise HTX and LTX services in Italy. Consensus was reached on a national LTX programme, under the supervision of NITp. Better coordination also resulted in HTX and paediatric transplants.
France	The Centre d'Evaluation de la Diffusion des Innovations Technologiques (CEDIT), part of the Assistance Publique des Hôpitaux de Paris, has issued several recommendations concerning organ transplant services in the Paris region. *Effect of the study* These are policy recommendations based on global evaluations. They had little effect on the policies of France-Transplant in the rest of France.
Finland	Several studies were conducted by the Nordic Expert Norway Committee on Transplantation, eg in 1986 on 'The restructuring of Scandia Transplant'. In 1985 the Scandinavian Liver Transplant Club reported on a supra-national programme for LTX. *Effect of the study* These studies are part of the Nordic collaboration within highly specialised health services, supported by the Nordic Council of Ministers. They are not technology assessments, but studies in feasibility and organisation of transplant services. Their effect on political decision-making is important.
Portugal	1986: study by the National Committee for Dialysis and Transplantation. *Effect of the study* The study laid the foundation for a national programme by the central health authorities for kidney transplants, dialysis facilities and other transplant services. It was a study on the feasibility of national coordination. The effects cannot yet be assessed.

Comments

No assessment studies (cost-benefit, cost-effectivess or quality-of-life studies) in organ transplantation have been conducted, as far as we know, in Belgium, FRG, Luxembourg, Spain, Switzerland, Austria, Greece or Turkey. Some international studies on organ transplantation cannot be regarded as technology assessments as such, but have had some influence on decision-making concerning organ transplant services. These are the multi-centre studies and international registries on a European or even global scale:

- Scandia Transplant multi-centre studies on kidney, heart and liver transplantation;
- Eurotransplant Kidney Transplant Registry: long-term follow-up of results in all 54 transplant centres;
- Collaborative Heart Transplant Study by G Opelz (Heidelberg) on the effect of HLA matching and blood transfusions;

- the European Liver-transplant Registry, started in 1985 and coordinated by H Bismuth (Villejuif, France);
- the International Registry for Heart Transplantation, coordinated by M P Kay (Minneapolis).

The data from these studies and registries influence the decision-making and policies of transplant centres as well as health authorities, because they come from a large database.

Some European organisations also disseminate the results of evaluation studies to their members, giving comments on the relevance for policy-making in transplantation. The most important are:

- EDTA (the European Dialysis and Transplant Association, now the European Renal Association);
- ESOT (the European Society for Organ Transplantation);
- ETCO (the European Transplant Coordinators Organisation).

7.9.2 Some case-reports

The Netherlands

In the early 1980s the Dutch Ministry of Health became very concerned about the sharply rising expenditure in health care, and they studied different approaches and options for cost-containment policies. One such measure was to block the 'automatic' introduction of new health technologies into the social insurance health benefit package. The proposal was to permit no reimbursement of new major health technologies before an in-depth evaluation study had been completed. Liver transplantation (which had already started) and heart transplantation (which was on the brink of being introduced) were selected as pilot projects. The Ministry of Health commissioned studies of the scientific 'state-of-the-art' from the National Health Council. On the basis of these reports both heart and liver transplantation were funded by special

research grants to study their cost-effectiveness. One LTX centre and two HTX centres were allowed to provide transplant services and were included in the study. The grants came from the National Sickness Fund Council, which is the decision-making body on reimbursement of health care costs. The studies were conducted by the Institute for Medical Technology Assessment at the University of Rotterdam and completed in 1988. On the basis of these reports the Minister of Health decided to admit heart transplantation as a regular health service, to be reimbursed by the social insurance. Liver transplantation was not admitted, but new grants were provided to continue the study.

Sweden

Heart and liver transplantation had already started in Sweden in 1984 (Stockholm and Göteborg centres). But the donor organs used in those procedures were not from ventilated, brain-death donors as was usual elsewhere, but from non-heart-beating donors, or imported from Finland, because at that time the brain-death criterion was not legally approved in Sweden. Nothing was officially done to control this situation until 1987, when the National Board of Health convened a committee to prepare a report on heart and liver transplantation in Sweden. It was no coincidence that new legislation on brain-death and organ donation was in preparation. The committee reported in 1988; it recommended a strict approach to the diffusion of heart and liver transplant centres, and a high degree of concentration of transplant services to optimise quality. The National Board asked the Association of Swedish County Councils to prepare a list of possible candidates for heart and liver transplant programmes. Two centres for liver transplantation and one (later followed by a second) for heart transplantation were selected. Other transplant centres are not allowed or reimbursed.

Ireland

Before 1985 any Irish resident in need of heart or liver transplantation had to travel abroad for such treatment. By 1985 the cardiac team of the National Cardiac Centre in Dublin felt that it would be in a position to carry out heart transplants. The unit was approved by the Department of Health after a feasibility and cost study had been performed. The unit did its first heart transplant in the autumn of 1985.

With liver transplantation the story was different: in the autumn of 1985 the first liver transplant was performed in Ireland by a surgical team in Dublin; within weeks a second team (unconnected with the first) did another transplant. There was concern that a small country should have two teams performing liver transplantation without any coordination. To tackle this problem a feasibility study was conducted. An independent expert was called in; this was a leading hepatologist from the UK who was invited by the Department of Health to give his judgement on the dilemma. He recommended that there was need for only one unit (doing both adult and paediatric liver transplants) in Ireland. The national liver transplant unit was created in Spring 1986.

7.9.3 Conclusions

Amazingly few comprehensive technology assessments have been done on organ transplantation. And fewer still have been requested by the health authorities with the aim of supporting their policy decisions on the introduction, diffusion or reimbursement of organ transplants. Only the UK, Sweden and The Netherlands have conducted such assessments around the time of introduction of heart and liver transplantation in their countries. In these cases it is clear that the studies did influence the policy decisions.

Equally amazing is the fact that few of the results of these studies have been used by health authorities in other countries, while preparing their own policies on introducing or diffusing transplantation. The best-known studies were those from the USA as well as the heart transplant study from the UK. However, in a number of countries studies were performed on organ transplantation that can be described as 'feasibility studies', in which the requirements and costs of a national transplant programme were outlined. These have influenced the diffusion of transplant technology in those particular country to a certain extent. Remarkable is the fact that a number of countries, where heart and liver transplantation have diffused considerably (such as FRG, Belgium, Austria, Switzerland and France) have put no effort into assessment studies of organ transplantation and have produced no evidence to underpin the national policies.

REFERENCES

1 Oregon Health Services Commission. Preliminary Report of March 1, 1990. State of Oregon, US, 1990.

2 Carrel A, Guthrie CC. Successful transplantation of both kidneys from a dog into a bitch with removal of both normal kidneys from the latter. *Science* 1906; 23: 394–5.

3 Carrel A. Remote results of the replantation of the kidney and the spleen. *J Exp Med* 1910; 12: 146–50.

4 Landsteiner K. Über Agglutinationserscheinungen normalen menschlichen Blutes. *Wien klin Wochschr* 1901; 46: 1182–4.

5 Medawar PB, Billingham RE, Brent L. Actively acquired tolerance of foreign cells. *Nature* 1953; 172: 603–6.

6 Dausset J, Ivanyi P, Ivanyi D. Tissue alloantigens in humans: identification of a complex system (Hu-L). *Histocompatibility Testing, Series Haemat* 11:51–62. Munksgaard, Copenhagen 1965.

7 Dausset J, Rapaport FT, Ivanyi P et al. Tissue alloantigens and transplantation. *Histocompatibility Testing, Series Haemat* 11:63–72. Munksgaard, Copenhagen 1965.

8 Rood JJ van, Leeuwen A, Bruning JW et al. The importance of leukocyte antigens in renal transplantation. Advances in Transplantation (Proc 1st Intl Cong Transplantation Soc, Paris 1967), ed J Dausset et al. Munksgaard, Copenhagen 1968, pp 213–20.

9 Schwartz R, Dameshek W. Drug-induced immunological tolerance. *Nature* 1959; 183: 1682.

10 Schwartz R, Dameshek W. The effects of 6-mercaptopurine on homograft reactions. *J Clin Invest* 1960; 39: 952–8.

11 Calne RY. The rejection of renal homografts: inhibition in dogs by 6-mercaptopurine. *Lancet* 1960; i: 417.

12 Borel JF. Immunological properties of cyclosporin A. *Heart Transpl* 1982; 1: 237–42.

13 Borel JF, Lafferty KJ. Cyclosporine: speculation about its mechanism of action. *Transpl Proc* 1983; 15: 1881–5.

14 Borel JF, Feurer C, Gubler HV et al. Biological effects of cyclosporin-A: a new anti-lymphocytic agent. *Agents Actions* 1976; 6: 468–75.

15 Borel JF, Feurer C, Magnee C et al. Effects of the new anti-lymphocyte peptide cyclosporin-A in animals. *Immunol* 1977; 32: 1017–25.

16 Calne RY, White DJ, Thiru S et al. Cyclosporin A in patients receiving renal allografts from cadaver donors. *Lancet* 1978; ii: 1323–7.

17 Calne RY. The development of immunosuppressive therapy. *Transpl Proc* 1981; 13(suppl.1): 44–9.

18 European Dialysis and Transplant Association. 19th Combined report on regular dialysis and transplantation in Europe, 1988, and Proceedings of the EDTA, Reports 1975–1987, vols. 9–21.

19 Organ Transplantation: issues and recommendations. Report of the Task Force on Organ Transplantation, April 1986. US Department of Health and Human Services.

20 Ullman E. Experimentelle Nierentransplantation. *Wien klin Wochschr* 1902; 15: 281–3.

21 Moore FD. Transplant: the give and take of tissue transplantation. Simon and Schuster, New York, 1972.

22 Jaboulay M. Greffe de reins au pli du coudre par soudures artérielles et veineuses. *Lyon Med* 1906; 107: 575.

23 Unger E. Nierentransplantation. *Klin Wochschr* 1910; 1: 573; Tissue and organ transplantation. *Ann Surg* 1914; 60: 195.

24 Morel C, Papin E. Les applications physiologues et chirurgicales des transplantations rénales. *Biol Med* 1913; 11:397.

25 Neuhof M. The transplantation of tissues. Appleton and Co, New York, 1923: 260–3.

26 Voronoy U. Sobre el bloqueo del aparato reticuloendotelial del hombre en algunas formas de intoxication por el sublimado y sobre la transplantacion del rinon cadaverico como metodo de tratamiento de la anuaria consecutiva a aquella intoxicacion. *Siglo Med* 1936; 97: 296.

27 Lundsteiner F, Hufnagel R. *Cited in* Hume DM. Experience with renal homotransplantation in the human: report of nine cases. *J Clin Invest* 1955; 34: 327.

28 Lawler RH, West JW, McNulty PH et al. Homotransplantation of the kidney in the human. *J Am Med Assoc* 1950; 144: 844–5.

29 Lawler RH, West JW, McNulty PH et al. Supplemental report of a case. *J Am Med Assoc* 1951; 147: 45–6.

30 Servelle M, Soulie P, Rongeulle J et al. La greffe du rein. *Rev Chir* 1951; 70: 186.

31 Dubost C, Oeconomos N, Nenna A et al. Résultats d'une tentative de greffe rénale. *Bull Soc Med Hop Paris* 1951; 67:1372.

32 Kuss R, Teinturier J, Milliez P. Quelques essais de greffe de rein chez l'homme. *Mem Acad Chir* 1951; 77: 755.

33 Hume DM, Merrill JP, Miller BF. Homologous transplantation of human kidneys. *J Clin Invest* 1952; 31: 640.

34 Hume DM, Merrill JP, Miller BF et al. Experiences with renal homotransplantation in the human: report of nine cases. *J Clin Invest* 1955; 34: 327.

35 Hamburger J, Vaysse J, Crosnier J et al. Transplantation d'un rein entre jumeaux non monozygotes après irradiation du receveur. *Presse Méd* 1959; 67: 1771.

36 Hume DM, Merrill JP, Miller BF et al. Experiences with renal homotransplantation in the human: report of nine cases. *J Clin Invest* 1955; 34: 327.

37 Murray JE, Merrill JP, Harrison JH. Renal homotransplantation in identical twins. *Surg Forum* 1955;6:432–6; Idem, Kidney transplantation between seven pairs of identical twins. *Ann Surg* 1958; 148: 343.

38 Terasaki PI (ed). Clinical Transplants 1988 and Clinical Transplants 1989. UCLA Tissue Typing Laboratory, Los Angeles, 1988 and 1989.

39 Shumway NE, Stinson EB. Two decades of experimental and clinical orthotopic homotransplantation of the heart. *Persp Biol Med* 1979; 22: 581–8.

40 Baumgartner WA, Reitz BA, Oyer PE et al. Cardiac homotransplantation. *Curr Probl Surg* 1979; 16: 2–61.

41 Griepp RB, Ergin MA. The history of experimental heart transplantation. *Heart Transpl* 1984; 3: 145–51.

42 Mann FC, Priestly JR et al. Transplantation of intact mammalian heart. *Arch Surg* 1933; 26: 219–24.

43 Demikhov VP. Experimental cardiac transplantation. *Byull Eksp Biol Med* 1950;4; Experimental transplantation of vital organs. (B Haigh transl). Consultants Bureau, New York, 1962.

44 Sinitsin NP. A transplantation of the heart. (Russian text) *Klin Med Mosk* 1953; 31: 5.

45 Marcus E, Wong SN, Luisada AA. Homologous heart grafts: transplantation of the heart. *Surg Forum* 1951; 2: 212.

46 Marcus E, Wong SN, Luisada AA. Homologous heart grafts. *Arch Surg* 1953; 66: 179–91.

47 Downie HG. Homotransplantation of the dog heart. *Arch Surg* 1953; 66: 624–36.

48 Webb WR, Howard NS. Cardiopulmonary transplantation. *Surg Forum* 1957; 8: 313.

49 Webb WR, Dequzman O, Hooper JF. Cardiopulmonary transplantation: experimental study of current problems. *Am J Surg* 1961; 27: 236.

50 Goldberg M. Homologous transplantation of the canine heart. *J Int Coll Surgeons* 1958; 30: 575.

51 Lower RR, Shumway NE. Studies on orthotopic homotransplantation of the canine heart. *Surg Forum* 1960; 11: 18.

52 Lower RR, Dong E, Shumway NE. Suppression of rejection crises in cardiac homografts. *Ann Thorac Surg* 1965; 1: 645.

53 Lower RR, Dong E, Glazener et al. Electrocardiograms of dogs with heart homografts. *Circulation* 1966; 33: 455–60.

54 Hardy JD, Chavez CM. The first heart transplant in man: historical reexamination of the 1964 case in the light of current clinical experience. *Transpl Proc* 1969; 1: 717.

55 Hardy JD, Chavez CM, Kurrus FD et al. Heart transplantation in man: developmental studies and report of a case. *J Am Med Assoc* 1963; 188: 1132–40.

56 Barnard CN. The operation. A human cardiac transplantation: an interim
report of a successful operation at Groote Schuur Hospital, Cape Town. *S Afr Med J* 1967; 41: 1271–4.

57 Barnard CN, Pepper CB. One life. Macmillan, New York, 1969.

58 Moore FD. Therapeutic innovation: ethical boundaries in the initial clinical trials of new drugs and surgical procedures. *In* Freund (ed). Experimentation with human subjects. New York, 1970: 358–78.

59 Shumway NE. Recent advances in cadaveric transplantation. *Transpl Proc* 1983; 15: 1221–4.

60 Austen WG. Heart transplantation after 10 years. *N Eng J Med* 1978; 298: 682.

61 Calne RY. The development of immunosuppressive therapy. *Transpl Proc* 1981; 13(suppl 1): 44–9.

62 Oyer PE, Stinson ED, Jamieson SW et al. Cyclosporin A in cardiac allografting. *Transpl Proc* 1983;15:1247–52 and 1983;15(suppl 1):2546–52.

63 Austen WG, Cosimi AB. Editorial retrospective: heart transplantation after 16 years. *N Eng J Med* 1984; 311: 1436.

64 Evans RW, Manninen DL, Overcast TD et al. The National Heart Transplantation Study: final report. Battelle Human Affairs Research Centres, Seattle, Washington, 1984.

65 Buxton MJ, Acheson R, Caine N et al. Costs and benefits of the heart transplant programmes at Harefield and Papworth Hospitals. DHSS Research Report no. 12. HMSO, London, 1985.

66 Bonsel GJ, de Charro FT, Habbema JD et al. De kosten en effecten van harttransplantatie. Erasmus Universiteit, Rotterdam, 1987.

67 Terpstra OT. The role of auxiliary liver transplantation. *Transpl Proc* 1987; 19: 4370.

68 Cannon JA. Liver transplantation. *Transpl Bull* 1956; 3: 7.

69 Starzl TE. Homotransplantation of the liver in humans. *Surg Gynecol Obstet* 1963; 177: 659.

70 Garnier H, Clot JP, Bertrand M et al. Liver transplantation in the pig: surgical approach. *In* Read AE (ed). The liver. Butterworth, London, 1967; 333–6.

71 Starzl TE, Groth CG, Brettschneider C et al. Orthotopic homotransplantation of the human liver. *Ann Surg* 1968;168:392–415.

72 Calne RY (ed). Liver transplantation: the Cambridge–King's College experience. Grune & Stratton, New York, 1983.

73 Starzl TE, Thiel D van, Iwatsuki S et al. Extended survival in human orthotopic liver transplantation. *J Am Med Assoc* 1988; 260: 2542–4.

74 Stocking B (ed). Expensive medical technologies: regulatory and administrative mechanisms in Europe. Oxford University Press, Oxford, 1988.

THE INTRODUCTION AND ASSESSMENT OF HEART AND LIVER TRANSPLANTATION IN THE NETHERLANDS

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HEALTH POLICY MAKERS IN THE NETHERLANDS

Decision making in The Netherlands health care system occurs at so many levels that some doubt the capacity of the system to reach rational decisions.[1]

Under article 18 of the Hospital Provisions Act the government has the power to limit and control the supply of certain listed expensive health provisions, including renal dialysis and kidney transplantation, radiotherapy, and cardiac catheterisation. The present list[2] dates from 24 November 1983; it seems probable that it will soon be extended to include heart transplantation.

Regular health care is normally paid for by the Sickness Funds and private insurance companies. These institutions are entitled to decide on their own initiative to pay for items of health care which are not named in the Hospital Provisions Act. The institutions coordinate their policy via their national organisations, the Association of Dutch Sickness Funds (VNZ) and the Royal National Association of Private Insurance Companies (KLOZ). Provided they can increase insurance premiums enough to cover their costs these institutions are not greatly interested in restricting the provision of health care.

The separation of responsibilities for planning and financing of health care results, of course, in weak control of the supply of health care. Sometimes this is advantageous, as in the case of renal dialysis, where government officials accepted it as desirable but had not the means or resources to adapt existing regulations quickly to the changing pattern of the End Stage Renal Disease Programme, so that in 1980–87 the amount of dialysis delivered exceeded the maximum which had been specified as eligible for repayment.[3] In the case of heart transplantation several Dutch patients received treatment outside The Netherlands and were reimbursed by regional Sickness Funds, without any policy decision about the usefulness of the procedure. Where the regional Sickness Fund refused to pay, some municipal authorities agreed to pay out of the Social Security Funds which are under their control. These ad hoc arrangements for transplantation abroad tended to set a precedent for transplantation programmes in The Netherlands itself.

Because the Sickness Fund Council supervises Sickness Funds and makes recommendations to the Government concerning the provisions sick fund patients are entitled to, this Council has some influence on the introduction and diffusion of high technology in health care. It also provides substantial funding for health technology assessment, and as a result proved highly influential during the introduction of heart and liver transplantation.

Recommendations about the introduction and diffusion of high medical technology in the Netherlands are traditionally made by the Health Council (HC), which is legally responsible for issuing reports, either on request by the Secretary of State for Health or on its own initiative, on developments in

[1] References, p 113.

medical science and technology. Reports of the Health Council are drafted by its secretariat in consultation with experts in the field.

The Health Council has played a pioneering role in cost-effectiveness studies. As long ago as 1972 it issued a report on costs and effects of the End Stage Renal Disease Programme, and in 1977 it initiated a similar study of kidney transplantation. In 1982 a fresh commission was established to make recommendations as to the development of the End Stage Renal Disease Programme. However, in the case of heart and liver transplantation the Health Council was given no resources for technology assessment. Although Health Council Commissions on heart and liver transplantation existed during the period in which technology assessments of heart and liver transplantation were carried out, they did not actively participate in them, with the result that the impact of those commissions on the studies has been less then optimal, despite the untiring efforts of its capable secretary to compensate.

DIFFUSION OF HEART AND LIVER TRANSPLANTATION IN THE NETHERLANDS

Thus the main institutional agents in the course of the introduction of heart and liver transplantation were the Department of Welfare, Health and Culture (DWHC), the Sickness Fund Council (SFC) and the Health Council (HC).

Important actors in the process of *technology assessment* were, of course, the institutions where the heart and liver transplantations were performed and the research groups involved in the assessment studies. The Academic Hospital of Groningen (AZG) deserves special notice, for several reasons:

- it initiated the liver transplant programme and was strongly committed to it
- it aimed to perform its own technology assessment of liver transplantation and to use this programme to develop its potential in the field of technology assessment. This policy was not fully compatible with the intention of national policy makers to separate delivery of a service from its assessment
- it embarked at an early stage on a heart transplantation programme, being in a position to organise one before other institutions
- it submitted requests to the Department of Science and Education to fund its programmes on both heart and liver transplantation
- its General Manager is a keen policy-maker, both within the hospital and as an external lobbyist representing the hospital's interests in political circles.

While the powers of the government over the introduction of medical technology are limited, it should be recognised that the government plays a subtle and decisive role in many processes. Thus, in the course of the discussion about the introduction and diffusion of heart and liver transplantation:

- the Department of Science and Education refused to provide separate funding for the programmes

- the DWHC refused to provide funding for the programmes

- the DWHC requested the Sickness Fund Council to provide funding for the programmes during an interim period, during which technology assessments could proceed
- the DWHC requested the Health Council to commission reports on heart and liver transplantation
- the DWHC informed the Dutch Parliament about the introduction and evaluation of heart and liver transplantation.

The history of events occurring during the introduction of heart and liver transplantation in the Netherlands reflects the emergence of a pattern which enabled the institutions involved in health technology policy to coordinate their policies, which gives some hope that the policy framework will be serviceable outside the field of heart and liver transplantation. Three periods can be distinguished:

- the period during which coordination was absent (1978–83)
- the period during which a joint policy was developed (1984–5)
- the period during which evaluation studies were carried out and policy decisions were made (1985–9).

In the first period the AZG started a liver transplantation programme and became one of the four leading liver transplant centres in the world. This programme was funded from the regular budgets of the hospital and the University of Groningen. Important factors within the AZG were the physicians involved, especially the head of the liver transplant department, C H Gips,and the surgeon, R A F Krom. Their careers and prestige were dependent on the development of the liver transplant programme and they were prepared to use all means to defend the programme and to obtain funds from the authorities.[4] In 1982 the hospital management informed the national authorities that its internal budgets were insufficient to continue the liver transplantation programme and applied for external funding by the Department of Science and Education. At that time about 12 liver transplants had been performed and it would not have been possible to halt the programme without inducing a lively discussion in the media.

In 1981 the AZG launched initiatives to introduce heart transplantation in Groningen. Haagen and Eijsman from the Department of Cardiology and Cardiosurgery visited Stanford, wrote a report and started discussions on the organisation of a heart transplantation programme in Groningen. A charitable foundation (the J K de Coel-Stichting) and Sandoz AG Netherlands funded the study. In 1982 Haagen and Eijsman reported that the AZG would be able to perform the first heart transplantation within six weeks of appropriate authorisation. In 1982 the management of the hospital applied to the Department of Science and Education for another supplementary grant.

Heart transplantation, at that time not a procedure performed in Dutch hospitals, became the subject of intense competition between the hospitals where cardiac surgery was performed. The five heart surgery centres, cooperating in the Advisory Committee on cardiac surgery, tried – at the request of the Secretary of State for Health – to reach agreement on the

centre(s) in which heart transplantation might best be developed. Haagen (AZG) and Penn (Academic Hospital, Utrecht) investigated the facilities and capacities in the five centres. Their conclusion was that Utrecht should be at the top of the list for a heart transplantation programme, followed by Groningen. But agreement was not reached.

The Academic Hospitals of Rotterdam and Leiden were not satisfied with the recommendations of the Advisory Committee. On 23 June 1984 the first heart transplantation in the Netherlands in a human being was performed in Rotterdam, in cooperation with the Academic Hospital of Leiden. In the press and in parliament questions were raised, and the Secretary of State publicly expressed his disapproval. Despite this Rotterdam was allowed to develop its heart transplantation programme; in September 1984 official permission to do so was received. In 1985 Utrecht was allowed to be a second transplant centre. Funding was guaranteed under article 52 of the Law on Special Health Care Costs, conditional upon cooperation with assessment of the programme during its first three years.

The AZG was unable to obtain external finances for its liver transplantation programme in 1983. The application for external funding was referred to the DWHC and to the Secretariats of the SFC and of the HC. In 1983 consensus gradually emerged between the DWHC and the SFC that new, high-cost technologies should not be covered by regular insurance unless the social implications had been assessed. Liver transplantation was clearly a treatment where evidence on the social implications was insufficient. A consensus conference in the United States recommended a wider application of liver transplantation but explicitly stated also that to gain 'its full therapeutic potential . . . the procedure must be the object of comprehensive, coordinated and ongoing evaluation'[5]. In the course of 1983 the AZG faced increasingly pressing requests to permit technology assessment as a condition for financial support for the liver transplantation programme itself. In May 1983 the AZG applied for funding of both the liver transplantation programme and a technology assessment, to be carried out by the hospital/university itself. It became evident that an independent assessment of the liver transplantation programme by this research team alone would be difficult to guarantee.

The second period (1984–5) saw a consensus reached between policy makers to the effect that:

- limits should be imposed on the automatic inclusion of new provisions in health care
- social aspects of important new technologies should be assessed to enable rational decisions about their introduction and diffusion
- heart and liver transplantation are subjects meriting assessment
- assessments are justified by the practical problems arising from the cut-throat competition among cardiac surgery centres to mount a heart transplantation programme and by the problems posed by the non-stop liver transplant policy of the AZG
- evaluation of heart and liver transplantation would be useful as a model for health technology assessment.

In December 1983 the SFC issued a report 'Limits to Care' in which a policy was enunciated which would prevent the automatic inclusion of new high-cost technologies in insured health care provision. Technology assessment would have to play a vital role in the consideration of candidates for health insurance cover. In the same month the Secretary of State for Health requested reports on heart and liver transplantation from the HC, seeking answers to questions about indications for each kind of transplantation, its cost and effectiveness, the desirability of its inclusion in the insured categories, the organisational requirements for its performance and whether it should be listed under article 18 of the Law on Hospital Provisions.

The Health Council rather quickly issued interim reports both on liver transplantation (January 1984)[6] and on heart transplantation (July 1984)[7]. In both cases it recommended performance of technology assessment, during which the liver transplantation programme in Groningen could be continued for up to two years. Subjects of study were to be cost-effectiveness, patient selection criteria, and optimal timing of the operation. A provisional Dutch heart transplantation programme could be initiated in one centre. By 6 July, when the report was published, the choice of the preferred centre had been pre-empted. According to the findings of the Advisory Committee on cardiac surgery and supposedly also of the majority of the Health Council Commission, Utrecht would be that centre, but the first heart transplantation had been performed on 23 June in Rotterdam. So reality took its course.

During 1984 the HC and the SFC negotiated the control of the evaluation studies. Since the studies were to be financed by the SFC it set up steering committees to which reports had to be submitted. The committees consisted of officials involved in policy making and not of physicians with an expert knowledge about heart and liver transplantation. It was decided that:

- a research team at the Erasmus University (Rotterdam) would be charged with the technology assessment of heart transplantation and part of the technology assessment of liver transplantation. This research team was drawn from two groups in the university, the Institute of Community Health, with knowledge of the cost-effectiveness of screening for breast and cervical cancer, and the economics section of the faculty of law, with knowledge of the cost-effectiveness of the End Stage Renal Disease programme. This research team was independent of the Rotterdam heart transplant group
- a research team at the University of Groningen would collaborate in the technology assessment of liver transplantation
- the HC Commissions, where the expertise on medical aspects of heart and liver transplantation resided, would step back so as to guarantee independence of judgement on the study results.

At the end of 1984 the Erasmus University Rotterdam and the University of Groningen were invited to submit research proposals and on 22 August 1985 the SFC accepted their joint proposal. The studies took about three years. By the end of 1988 122 hearts and about 100 livers had been transplanted. Data about those transplants and about all patients referred to the centres for a

heart or a liver transplantation were used to estimate not only the cost-effectiveness of heart and liver transplantation but also the demand for heart and liver transplantation and the expected supply of donor hearts and livers.

In September and October 1988 final reports of the studies on liver and heart transplantation were submitted to the SFC. The results and the conclusions of the two studies differed considerably.

Heart transplantation was considered to be an expensive procedure, with a clear life-prolonging effect and a positive effect on the patient's quality of life. The cost per life-year gained was estimated at Dfl. 50,000. Rather courageously the researchers estimated the number of life-years gained by a heart transplant to be about 12, a conclusion that was heavily dependent on the assumption that the average probability of death three years after transplantation would be that actually observed. In any case, the costs per life-year gained did not change markedly if the number of life-years gained was reduced to six, a figure thought to be a conservative estimate. It was concluded that the demand for heart transplantation would exceed the supply of donor organs.

The liver transplantation study concluded that this was a still more expensive procedure than heart transplantation, with less certain life-prolonging effects: although it probably prolonged life in the group of patients with a poor score on the Child-Pugh index, this was not so for patients with better scores. Liver transplantation might be life-prolonging if the timing of the transplantation could be improved.

The SFC issued recommendations on the basis of these results to the Secretary of State for Health that heart transplantation should be included in the schedule of insured health care provisions and that the heart transplantation programmes in Rotterdam and Utrecht should continue. Liver transplantation, however, was not to be included. More evidence was thought to be necessary to support the view that improved selection of patients and timing of the procedure could increase the benefits of the procedure. Therefore, consideration of whether liver transplantation should be included would have to be deferred.

The Health Council Commissions, reporting in February and March 1989,[8,9] also recommended inclusion of heart transplantation in the schedule of regular health care provisions, and restriction of the number of centres where heart transplantation would be performed. Improvement of donor heart procurement was considered of great importance. Orthotopic liver transplantation was still to be considered an experimental procedure, and more evidence was necessary as to the selection criteria and timing of the procedure. Partial auxiliary liver transplantation was considered an experimental procedure which merited further development and evaluation.

CONCLUSIONS

The history of the introduction and diffusion of heart and liver transplantation in The Netherlands provides an example of how diffusion of a new technology may be brought under control.

After a period of poor control, political coordination was reached through agreement between the policy-making institutions on a moratorium on decision making. During this moratorium selected hospitals were allowed to

perform heart and liver transplantation on condition that they collaborated with an independent technology assessment.

For heart transplantation the moratorium stabilised a previously very unstable process of competition between centres. The process of technology assessment provided an opportunity for policy makers to meet frequently and to discuss many aspects and development outside a framework in which decisions had to be taken under political pressure. Modifications of the programme could be discussed rationally. Thus, during the period of technology assessment the Academic Hospital of Rotterdam proposed an extension of the programme to heart–lung transplantation. The communication structure which now existed was adequate to prevent the immediate introduction of heart–lung transplantation, which was thought by nearly everybody involved to be premature. In many other situations such a consensus has not prevented the introduction of a procedure by a hospital with a research commitment.

For liver transplantation the moratorium allowed for gradual rationalisation in the decision making process, which at the end of the evaluation study resulted in acceptance by the Academic Hospital Groningen of the rather disappointing conclusions about the life-prolonging effect of the procedure. In consequence a more gradual extension of liver transplantation could take place which reflects the uncertainties about the benefits of the procedure and allows controlled improvements to be introduced into the programme.

REFERENCES

1 De Charro FT, Banta HD. Transplant policy in The Netherlands. *Int J Technol Assessment Health Care* 1986; 2: 533–544.

2 Besluit bijondere functies Wet ziekenhuisvoorzieningen. Besluit van 24 November 1983 houdende vaststelling van een algemene maatregel van bestuur als bedoeld in article 18, eerste lid, van de Wet ziekenhuisvoorzieningen (Stb. 1971, 268, zoals laatstelijk gewijzigd bij Wet van 2 November 1978, Stb. 763). *Staatsblad* 1983, 742.

3 De Charro FT. Kosten-effectiviteitsanalyse van het Nierfunktievervangingsprogramma in Nederland (1988). Eburon, Delft.

4 Gips CH, Krom RAF. Development of the liver transplantatiopn team in Groningen. *In* Smit Sibinga CT et al. (eds). Transplantation and Blood Transfusion. Martinus Nijhoff, Leiden, 1984.

5 Consensus Conference on liver transplantation. *J Am Med Assoc* 1983; 250: 2961–2964.

6 Health Council. Interim recommendations on liver transplantation. January 27, 1984.

7 Health Council. Interim recommendations on heart transplantation. July 6, 1984.

8 Health Council. Report on heart transplantation. March 1989.

9 Health Council. Report on liver transplantation. March 1989.

HEART AND LIVER TRANSPLANTATION IN THE UNITED KINGDOM

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Christiaan Barnard performed his first successful heart transplant in 1968. That year the number of kidney transplants in Britain rose from 48 to 144, and the first moves were made to set up a nationwide matching scheme for donor organs. In an attempt to emulate Barnard's success, more than 100 hearts were transplanted in 22 countries during 1968. Most of these patients soon died, including the three done in London.

Although there was no policy statement at this stage no further transplants were performed in the UK during the next four years, when one more was done. Then the Chief Medical Officer of the DHSS declared that cardiac transplantation was still largely experimental and that specific resources for it should not at present be made available. This was in a letter sent in January 1973 to leaders of cardiac surgical teams and to hospital boards, and it listed the group of nine experts who had advised him. They also recommended that research related to transplantation be pursued with vigour, and that the progress of this and of the clinical programmes in the USA be closely followed for indications of when further developments might be appropriate. It was suggested that this might best be done by setting up a standing committee to advise the DHSS and its ministers. The Transplant Advisory Panel was established later in 1973 to advise on all aspects of transplantation. In addition to surgeons involved in transplantation of various organs (including the grafting of corneas) it included anaesthetists, neurosurgeons and physicians – representing those who were likely to be concerned with the care of potential donors.

Only the unit in Stanford, California continued to do heart transplants, on carefully selected cases. In January 1979 that unit reported[1] in the *British Medical Journal* (*BMJ*) that two-thirds of 150 heart transplant patients were alive after a year, most of whom survived for three years. These results, coupled with the acceptance in Britain of criteria for diagnosing brain death, led an anonymous editorialist in the BMJ to consider[2] that the time had come for the NHS to look again at this operation. In fact the DHSS has been under pressure during the previous two years to allow transplantations to start in the regional cardiac unit at Papworth. This was near Cambridge, where there were active renal and liver transplantation programmes (the first liver transplantation in Britain having been performed there in 1968). In 1977 the Transplant Advisory Panel set out criteria to be met by a centre wishing to embark on a programme of heart transplantation, and in February 1979 agreed that Papworth was suitable. Three patients had operations there that year, one of whom was to survive for five years. His surgeon, Terence English, was later to say that the acceptance of heart transplantation by the public and the authorities owed much to the way in which the cheerfulness and zest for life of Keith Castle captured the public imagination. That was possible only because the media were then still fascinated by stories about transplantation,

[1] References, p 123.

and this ensured that his successful survival soon became common knowledge throughout the country.

Although television was later to provide useful publicity for liver transplantation, the influence of the media was not always helpful. Indeed, organ donation from cadavers in Britain has suffered more than one serious setback following damaging publicity about the management of donors and supposed doubts about brain death.[3] The resulting shortage of donors affected renal transplantation, which was thereby prevented from expanding rapidly enough to keep pace with the increasing waiting list of patients on dialysis.

Yet the reason for the concern that affected organ donation was the absolute requirement that hearts and livers for transplants be removed from heart-beating donors. At the same time, however, surgeons involved only in renal transplantation were mostly coming to prefer kidneys taken from brain-dead patients who were still on the ventilator. Not only did this make for better quality organs but it made arrangements for the removal of organs much easier, obviating the need to wait until the heart stopped and then performing rapid surgery. The other factor which has limited the scale of adoption of heart and liver transplantation in the UK has been concern about the impact that these procedures make on the limited resources available to the NHS. These two concerns, about brain death and about costs, have been curiously combined in a campaign of dissent, from a tiny group of doctors who have been protesting continually since 1980.

ORGAN DONATION

Kidney transplantation using live donors began in Britain in 1956. In 1961 the Human Tissue Act extended to all organs the provisions already enacted in 1952 for corneas to be donated for grafting. The first cadaver kidney transplantation came the next year and by 1974 there were over 500 renal transplantations per year, 90 per cent of organs coming from cadavers (as was the case in most of Europe).

In 1972 the DHSS took over the running of the National Organ Matching Programme at Bristol (Southmead Hospital). This later became the UK Transplant Service (UKTS), which maintains a computer record of waiting recipients throughout the country, with details of their immunological status. When a potential donor is notified to this service, matches are made and transplantation teams are told which of their patients on the waiting list are well or moderately well matched to the donor. The UKTS publishes annual reports with detailed statistics of all donors that have been notified to the Service and transplants which have been performed; this report now includes chapters on heart and liver transplantation.

In 1972 the DHSS also issued donor cards to be carried by those wishing to donate their kidneys or corneas in the event of accident, and there have been many updates and variations of this. Although several opinion polls show that more than three-quarters of the population are in favour of organ donation, a poll in 1987 found that only 22 per cent of the sample possessed a card and that only 14 per cent had it with them when interviewed.[4]

In practice it seems that the carrying of a card is seldom what initiates

donation. The continuing concern to increase the number of kidneys available has led to repeated discussions about opting-out legislation, but this has never gained wide support among doctors, the public or parliament. Several local opting-*in* schemes have been developed; these are usually linked to donor cards, which include a slip to be returned for registration on a local health authority computer. The card records the willingness of the holder to have organs removed after death, and there is now space to indicate whether all organs are available, or only those specified by the card holder. Because the programmes for heart and liver transplantation have so far been limited the availability of these organs has not yet become a major problem, except for children. Only a fraction of the 800 kidney donors each year would need to give a heart and/or liver to allow the 200 or so of each that are currently required; indeed, more offers are currently made than can be taken up. This is because almost 65 per cent of donors of internal organs now allow several organs to be taken (Table 1).

Table 1
Restrictions placed by donors on organs that may be removed

	Only kidney	Only heart	Only liver	Only cornea	Internal organs	Any organs
1986	420	27	7	304	861	407
1987	311	38	4	397	859	506

Table 2
Transplantations performed in the UK 1979–87

	Kidney	Heart	Heart & Lung	Liver
1979	851	3		
1980	871	25		
1981	784	26		
1982	1085	36		
1983	1182	53	1	20
1984	1552	116	10	51
1985	1485	137	37	88
1986	1586	176	51	127
1987	1558	244	72	175

DEVELOPMENT OF BRAIN DEATH CRITERIA

The Human Tissue Act did nothing to define death, and the assumption was that this had to be determined by the traditional criteria of cessation of heartbeat and breathing. 'Brain death' had been described in 1959 in Paris,[5] but it was almost 10 years before the Harvard criteria for brain death were published[6] – in 1968, the busy heart transplantation year. Two years later,

Kansas passed the first brain death law, accepting neurological criteria for death. It was not until 1974 that such a law was passed in California, where the Stanford heart transplantation programme had already been active for seven years. During the early 1970s several hospitals in the USA produced local criteria or codes of practice for the diagnosis of brain death, varying only in detail from those from Harvard. However, in 1971 neurosurgeons in Minnesota, reporting their experience since 1967, indicated that brain death could be reliably diagnosed on clinical grounds alone, and that an EEG was not only unnecessary but could be misleading.[7]

The first statement about British practice was in an anonymous editorial in *The Lancet* in 1974, which mentioned that one large neurosurgical unit had adopted the Minnesota criteria in 1972.[8] This editorial detailed how brain death should be diagnosed, and it stressed that it was in the interests of everyone concerned to make an early decision to discontinue ventilation of the patient once such a diagnosis had been made. The editorial made no mention of organ donation or transplantation, which is significant in view of later accusations that brain death had been 'invented' in response to the needs of transplantation programmes. The neurosurgeon who wrote the following year in the *Journal of Medical Ethics* on the recognition and management of brain death did, however, face this issue: his title was 'The Donor Doctor's Dilemma'.[9] That same year a discussion document on 'The Shortage of Organs for Transplantation' was published (in the *BMJ*) by the British Transplantation Society.[10] It came from a broadly based committee which included a lawyer, a coroner, a bishop and a neurosurgeon; transplantation surgeons were in a minority. Emphasising that brain death was now accepted in the USA, France, FRG, Belgium, Denmark and Switzerland, it urged that Britain should embrace the concept more formally. It included a summary of the criteria from the two papers just referred to.

Meanwhile, a working party set up in 1973 by the Transplant Advisory Panel of the DHSS had produced a set of diagnostic criteria for brain death. These were sent in 1974 by the Chief Medical Officer to the medical Royal Colleges for comment. The final document, 'Diagnosis of Brain Death', was eventually published in November 1976 in both *The Lancet* and the *BMJ*.[11] It made no mention of transplantation and provoked no adverse comment. In January 1979 the Colleges published in both journals a memorandum with the same title which stated explicitly that 'brain death represents the stage at which a patient becomes truly dead whether or not the function of some organs, such as the heart beat, is still maintained by artificial means'.[12]

In October of that year the DHSS published 'A Code of Practice for the removal of cadaveric organs for transplantation'.[13] This had been produced by a working party which included many members who had previously been on the brain death group. It reprinted the full text of the Human Tissue Act and the two Royal College documents, but it was primarily a practical handbook for those involved, and it was sent to all relevant NHS personnel. It included clear advice about approaching relatives and informing the coroner, with checklists for administrative and legal measures, for diagnosing brain death and for the removal of organs. A revised version was published in 1983, but there were no changes to the criteria for brain death.[14]

Some academic lawyers subsequently argued in various journals about the interpretation of parts of the Human Tissue Act. They were concerned about who in various circumstances was the person lawfully in charge of the body; about the degree of obligation to seek out relatives to give permission for removal or organs, and about the rights of relatives to override the wishes of a deceased person who had signed a donor card. However, it was generally agreed that no legislative change was necessary, and that remains so more than a decade later. As one lawyer said, 'In Britain you are dead when a doctor says you are dead, and the law asks no questions about how the doctor reached that decision.'

DISSENT ABOUT BRAIN DEATH AND HEART TRANSPLANTS

Although the widely publicised documents from the Royal Colleges had provoked no adverse comment, this proved to be the calm before the storm. By the end of 1980, two centres had between then performed 25 heart transplantations. In the spring of that year a *Lancet* editorial had little doubt that this operation did prolong life of good quality.[15] It considered that the main debate now was about how many transplantations could be afforded, whilst the least troublesome issue raised by the success of cardiac transplantation was the ethics of removing a beating heart. This assertion was challenged in a letter from two doctors, one of whom was a cardiologist.[16] They were concerned about the moral and ethical problems associated with the equating of brain death with death; about the certainty that the tests proved that every part of the brain was totally dead, about how soon after the cessation of vital functions the body could be traumatised for the sake of others. They went on to state 'we have no test for the presence or absence of the human spirit, wherever it may locally or generally reside'. They predicted that within a few decades renal and cardiac transplantation would be replaced by ethical alternatives provided by advances in bioengineering. None of these issues was taken up in the correspondence columns of *The Lancet*. However, this was to be but the first of repeated protests by Evans and two or three local supporters which were still to be heard nine years later. Over the years it has become apparent that this dispute may be as much to do with the diversion of resources (and attention) to cardiac transplantation as it is about brain death, because the objectors worked in one of the hospitals (Papworth) that is designated for cardiac transplantation.

The most significant consequence of that letter to *The Lancet* in April 1980 was that in October that year the BBC transmitted at peak time a programme attacking the brain death criteria. The dramatic title 'Transplants – Are the Donors Really Dead?' caught the attention not only of the millions who watched the programme, but those seeing the trailer article in the *Radio Times*. This 45-minute TV documentary asserted that the failure to use EEG tests made the British criteria unsafe. But the critics on the programme were American doctors, and the 'evidence' for doubting the diagnosis of brain death in Britain was a series of American patients who had survived after allegedly having been believed to be brain-dead. There was an immediate dramatic fall in the number of donors which affected the renal transplantation programme nationwide.

An unprecedented furore followed both in the medical and national press, with more than 30 letters each in *The Lancet* and the *BMJ* over the next few months.[3,17] There were questions in Parliament, and eventually the BBC agreed to an extended TV debate in February 1981. This was preceded by two films, made by the two opposing sides in the argument. In one of these some American doctors defended the British criteria (as a number had already done in the above-mentioned letters). But in the other film some European doctors appeared as additional critics of Britain, supporting the case for EEG tests. A report from three British neurosurgical units[18,19] did a lot to restore confidence. Later in 1981 the Royal Colleges decided not to revise the criteria as published in 1976. At about the same time national guidelines for the determination of death were published in the USA for the first time.[20] These corresponded closely to those in Britain, and they stressed that EEG and other laboratory investigations were not necessary, although they could be useful in certain circumstances.

The UK criteria were reviewed by the Colleges again in 1983 and in 1986, but no revision was found necessary. Noting this in a letter to *The Times* in January 1987 the chairman of the Conference of Royal Colleges commented 'We have repeatedly asked our critics to produce evidence that any patient has survived after brain death has been established by these criteria; this they have failed to do.' By that time Evans and another dissenting doctor had presented their case to a working party set up by the Royal College of Physicians to consider the supply of donor organs. Its report noted[21] that 'the difference between our views and theirs is in the concept of when death occurs'. In 1987 and 1988 the critics turned their attention to opposing attempts to introduce 'required request' to relatives of brain-dead patients for donation of organs. They also asserted that the donor card was 'a charade of consent'. They suggested that prospective donors should have more explanation about the term 'after my death'. If potential donors had any doubts they should in the view of these critics be encouraged to delete all but corneas and kidneys, and to specify that they do not wish to be heart-beating donors. A BBC TV programme 'The Gift of Life' in 1987 was attacked by these critics as being 'pure propaganda for organ transplants'. In April 1988 Dr Evans, the leading critic, took early retirement from Papworth at the age of 60. This gained him TV interviews and space in the national press to state yet again his objection to heart transplantation. He told one interviewer that retirement would allow him more time and more freedom of speech to carry on his campaign.

There was no doubt that that the 1980 TV programme caused a fall-off in organ donation. Further temporary reductions are believed to have been associated with some of the subsequent protests that reached the public press. It may well be that the slow growth in the number of donors over recent years has been related to the persistence of these critics in trying to sow doubts in the minds of the public and of uninformed members of the professions. However, a 1987 poll revealed that only 14 per cent of the public and 11 per cent of intensive care staff had any doubts about the diagnosis of brain death.[4] The effect of the shortage of donors is, however, still felt mainly by the renal transplantation programme – with its long waiting list. This is ironic because the critics have always claimed that they are not opposed to

kidney transplants, because they maintain that these could be done without heart-beating donors; in practice, hardly any renal transplant surgeon would now agree. What is evident is that, because of the shortage of cadaver kidneys there has been an increase in the use of live donors in Britain in the late 1980s, and that raises another set of ethical issues.

ECONOMIC ASPECTS OF HEART TRANSPLANTATION

In 1979 funding for all hospital services depended on Regional Health Authorities, which received annual block allocations from the DHSS for populations of 2–4.5 million. In 1978 the Cambridgeshire (District) Health Authority agreed to fund the first two transplants in 1979, but no more than that. Later that year the costs of a transplant were calculated as about $15,000 above those of an open heart operation. Funds were sought for a proposed programme of 10 operations per year using this as the cost basis. The next six operations were funded by the National Heart Research Fund. From then until the end of 1984 (39 transplants being done in that year) the programme was supported by special grants from the DHSS, a generous personal benefaction, and other local fund-raising. Meanwhile similar ad hoc support from a variety of sources had enabled the programme at Harefield Hospital (in North London) to develop under the leadership of Magdi Yacoub: 77 transplants were done there during 1984. It was only then that the DHSS accepted cardiac transplantation as eligible for supra-regional funding. This mechanism had been set up in 1983 to deal with a number of expensive innovative technologies each of which was supplied by a single Unit for a population of more than 5 million. Both centres active in heart transplantation were designated to receive such funds, and two others have since been approved. Expansion to nine centres is planned, and funds to support 500 transplants a year were announced in December 1988.

The decision to accept that heart transplantation should be centrally funded followed closely on the final report in February 1985 of a study[22] of the costs and benefits of the two established heart transplantation programmes. This had been commissioned by the DHSS in October 1981, and fortunately the health economists and community medicine specialists concerned insisted on securing sufficient funds for them to analyse outcome not only by survival but by quality of life (QOL) measures. There was a marked and favourable improvement in QOL after transplantation, most survivors being restored almost to normal QOL for their age. The survival rates were as good as those in Stanford, having improved considerably when cyclosporin was introduced in 1982 to minimise the risk of rejection of the transplanted heart. This drug also reduced the length of stay in intensive care after operation, which significantly reduced costs. Interesting differences in practice and costs between the two centres became apparent as the study progressed, and these led to changes that reduced costs further. There are few other procedures for which good data are available for comparisons of cost-benefit to be made with heart transplantation, but these are available for coronary bypass grafting and renal dialysis. In terms of cost per quality-adjusted life year gained, heart transplantation compares favourably with bypass grafting for coronary disease

that affects two vessels. It is considerably less expensive (in the first year) than one year's hospital dialysis and very much less costly in subsequent years. No comparable study has yet been made of liver transplantation in Britain.

A matter of some concern is the number of potential recipients who have to be investigated in order to select those who are suitable, and the extent to which the costs of those deemed unsuitable, or who die while waiting for a transplant, should be debited to the programme. The scale of this can be judged from nine years' experience at Papworth where 890 patients were referred, 534 admitted for investigation, 380 accepted and 247 eventually transplanted.[23] As criteria for acceptance are broadened to included more seriously ill patients for consideration, the cost/benefit ratio is likely to become less favourable. Not only will the costs of preparing such patients for operation be greater, but the success rate is likely to be less good. There is already evidence of this in a 1988 report from one of the UK units.[24] The British Cardiac Society estimated in 1984 that there might be 500 patients eligible for a heart transplantation each year under the age of 50 but noted that this number would rise exponentially if the age limit was allowed to rise.[25] But if other criteria were also relaxed the number would rise still more – and the aggregate cost of the heart transplantation programme could then become daunting. A recent estimate is for 1500–2000 heart transplants a year, with heart-lung transplants also rising considerably – especially as increasing numbers of patients with cystic fibrosis are surviving into adulthood.

LIVER TRANSPLANTATION

This procedure has excited much less emotion and interest than heart transplantation, and there is also less published about the programmes and their financing. Given the considerably lower level of funding of health care in the UK than in most other countries it seems a paradox that for several years Britain has had the largest liver transplantation programme in the world after that of Starzl in Denver. Of 450 livers transplanted in Europe in 1986, no fewer than 130 were done in the UK; several of these patients came from other countries in Europe under inter-governmental agreements. This has been due to the energy and enterprise of Roy Calne in Cambridge, but a second centre is now performing considerable numbers, and both are recognised for supra-regional funding by the Department of Health.[26,27]

Children have been accepted since 1983, but there is a problem in securing donors. When one particular child was waiting for a liver, a popular TV programme publicised his plight. Not only was an organ soon forthcoming, but there was an increase in donors in general for a time thereafter. Another concern is the demand for large amounts of blood for transfusing during the operation in a country where all blood donation is voluntary and where local shortages from time to time restrict even conventional surgery.

CONCLUSIONS

There is no doubt that organ transplantation is widely regarded in Britain as a worthwhile endeavour. Several opinion polls have shown this and have

confirmed the willingness of most people to accept the concept of brain death and to be prepared to consider organ donation. Reservations are mostly related to the perception that these are very costly procedures, and this applies particularly to other professionals. Thus, an opinion poll of several hundred British doctors in 1987 showed over 90 per cent in favour of kidney transplants and corneal grafting, but fewer than 50 per cent in support of heart or liver transplantation.

Sir Douglas Black, when president of the Royal College of Physicians of London, observed that advanced technologies were often a divisive force in medicine. With fixed budgets in the hospital sector it is inevitable that specialties which depend less on expensive technologies are often very critical of the resources that are allocated to other disciplines. Without any clear idea of the cost/benefit ratios involved, they are apt to assert that many more patients might have benefited from more mundane procedures for the cost of one transplant. Before the cost–benefit study of heart transplantation it was not uncommon for some doctors to describe expenditure on this operation as obscene when there were waiting lists a year long for hernias, hip replacements or cataracts. This may well be heard again if a large expansion of the transplant programme is proposed without there having been some improvement in meeting the needs of patients with less dramatic conditions for which effective procedures have been developed but are available for only a fraction of the patients who could benefit.

ADDENDUM 1990

The above account was completed in January 1989. In 1990, both heart and liver transplantation are flourishing, with numbers of centres and of operations (nationwide) increasing. There are now seven adult and three paediatric heart programmes, with five more in development; almost 400 operations were done in 1989, including 94 heart-lung transplants (39, lung only). About 300 livers were transplanted in five centres, with at least two more in development. An appreciable number of transplants are performed on nationals of other countries.

Several reports[28–30] on organ donation in 1990 show that in most cases of brain death relatives are now asked about donation, but that about 30 per cent refuse consent. These surveys suggest that the pool of unused brain-dead donors may not be large enough to meet increasing demands, but that if more patients with severe brain damage were ventilated for the purpose of securing organs there could be enough. Of almost 2000 kidney transplants, only 6 per cent came from live donors. An opinion poll of 2205 adults in their homes in May 1990 showed 72 per cent in favour of requiring doctors to request donation before turning off a life-support machine, and 60 per cent believed that all patients going into hospital for an operation should be offered a donor card to sign. Only 39 per cent considered that organs could be removed unless there was a specific recorded objection.[31]

It remains to be seen whether the newly emerging internal market in the National Health Service results in any rearrangement of priorities that favours an expansion of organ transplantation.

REFERENCES

1 Jamieson SW, Stinson EB, Shumway NE. Cardiac transplantation in 150 patients at Stanford University. *Br Med J* 1979; 1: 93–94.

2 Anon. Cardiac transplantation 1979. *Br Med J* 1979; 1: 69–70.

3 Jennett B. Brain death. *Br J Anaesth* 1981 ; 53:1111–1119.

4 Wakeford RE, Stepney R. Obstacles to organ donation. *Br J Surgery* 1989; 76: 435–439.

5 Mollaret P, Gordon M. Le coma dépassé. *Rev Neurol* 1959; 101: 3–15.

6 Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death. A definition of irreversible coma. *J Am Med Assoc* 1968; 205: 85–88.

7 Mohandas A, Chou SN. Brain death: a clinical and pathological study. *J Neurosurgery* 1971; 35: 211–218.

8 Anon. Brain damage and brain death. *Lancet* 1974; i: 341.

9 Jennett B. The donor doctor's dilemma: observations on recognition and management of brain death. *J Med Ethics* 1975; 1: 63–66.

10 British Transplantation Society. The shortage of organs for clinical transplantation: document for discussion. *Br Med J* 1975; 1: 251–255.

11 Conference of Medical Royal Colleges and their Faculties in the United Kingdom. Diagnosis of brain death. *Br Med J* 1976; 2: 1187–1188.

12 Conference of Medical Royal Colleges and their Faculties in the United Kingdom. Diagnosis of death. *Br Med J* 1979; 1: 332.

13 Health Departments of Great Britain and Northern Ireland. The removal of cadaveric organs for transplantation: a code of practice. HMSO, London, 1979.

14 Health Departments of Great Britain and Northern Ireland. Cadaveric organs for transplantation: a code of practice including the diagnosis of brain death. HMSO, London, 1983.

15 Anon. Cardiac transplantation: the second round. *Lancet* 1980; i: 687–688.

16 Evans DW, Lum LC. Cardiac transplantation. *Lancet* 1980; i: 934.

17 Anon. An appalling 'Panorama'. *Br Med J* 1980; 281: 1028–9.

18 Jennett B, Gleave J, Wilson P. Brain death in three neurosurgical units. *Br Med J* 1981; 282: 533–539.

19 Anon. Brain death. *Lancet* 1981; i: 363–364.

20 President's Commission. Guidelines for the determination of death. *J Am Med Assoc* 1981; 246: 2184–2186.

21 Conference of Medical Royal Colleges and their Faculties in the United Kingdom. Report of the working party on the supply of donor organs for transplantation. DHSS, London, 1987.

22 Buxton M, Acheson R, Caine N et al. Costs and benefits of the heart transplant programme at Harefield and Papworth Hospitals. DHSS Research Report No. 12. HMSO, London, 1985.

23 English TAH, Cooper DKC, Cory-Pearce R. Recent experience with heart transplantation. *Br Med J* 1980; 281: 699–702.

24 Mulcahy D, Wright C, Mockus L et al. Cardiac transplantation in severely ill patients requiring intensive support in hospital. *Br Med J* 1988; 296: 817–819.

25 British Cardiac Society. Cardiac transplantation in the United Kingdom. *Br Heart J* 1984; 52: 679–682.

26 Anon. Liver transplantation, 1985 and beyond. *Lancet* 1985; i: 27–28.

27 Neuberger J. When should patients be referred for liver transplantation? *Br Med J* 1987; 295: 565–566.

28 Gore SM, Hinds CJ, Rutherford AJ. Organ donation from intensive care units in England. *Br Med J* 1989; 299: 1193–1197.

29 Anon. Organ donors in UK – getting the numbers right. *Lancet* 1990; 335: 80–82.

30 Gentleman D, Easton J, Jennett B. Brain death and organ donation in a neurosurgical unit: an audit of recent practice. *Br Med J* 1990; 301: 1203–1206.

31 Which ? way to health. [Consumers' magazine] October 1990.

PLANS FOR HEART AND LIVER TRANSPLANTATION IN GREECE

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The heart and liver transplantation services started only in 1990 in Greece. The Greek National (Hellenic) Transplantation Service, which coordinates renal transplantation here, is actively involved in planning transplantation of the larger organs.

Liver transplantation is to take place in kidney transplant centres, and heart transplantation in departments of cardiac surgery. The renal transplant centre in Laikon Hospital, the University Department of Surgery in Aretaion Hospital (Athens) and the Cardiac Surgery Unit of Ippokration Hospital (Athens) are ready to start.

Special centres for such organ transplants are not planned. The National Health Council of Greece, the official body charged with planning health care developments, intends to increase the number of renal transplant centres and to establish centres for other organs. A questionnaire has been sent to seven large hospitals in different parts of Greece asking whether appropriate facilities exist there.

INFLUENTIAL ACTORS

The most influential actors in these developments have been doctors, acting either individually or as members of scientific societies or specific units. Hospitals may play either a positive or a negative role.

Before 1990, the media were active in asking why heart and liver transplantation had not yet been introduced, and interviews with specialists, especially kidney transplant surgeons, were held and publicised. Religious groups, by contrast, have had little effect. The Orthodox Greek Church accepts organ transplantation and it is well known that the Archbishop is an organ donor, but there has been no official Church campaign for or against heart and/or liver transplantation.

The National Health Council intends to promote heart and liver transplantation, as do 15 private associations. People willingly become organ donors: there are 37,000 organ donor card carriers in Greece. Appendix 1 gives recent data on kidney and cornea donations.

Costs

All costs, including that of the donor operation, are to be covered by the recipient's insurance, as they are for kidney transplantation. The insurance companies have not protested. When kidney transplantation is performed outside the EC some insurance companies have put a limit on the amount they will pay. In such cases the difference is covered by the Ministry of Health. (For kidney transplantation abroad a cost of 6–8 million drachmas is

accepted.) In the EC countries costs are paid in accordance with the EC–E112 form. There has been no cost-effectiveness or other evaluative study of heart or liver transplantation in Greece.

ORGAN PROCUREMENT: KIDNEYS AND CORNEAS

The Hellenic Transplant Service coordinates kidney procurement, and has already successfully introduced a multi-organ donor (MOD) scheme to identify potential donors of larger organs. There remains much coordinating work to do, and a special educational course to familiarise doctors working in intensive care units with the multi-organ donor has been organised.

No controversy has as yet arisen over definitions of brain death (which is accepted by the medical profession, with some exceptions), and no legal definitions have been introduced or changed. The first law concerning organ transplantation appeared in 1978 and was modified in 1983. By this law Greece adopted brain death as a criterion of death. According to the law, the organs of every person (whether or not a donor card carrier) certified brain-dead can be used for transplantation, with the sole exception of persons who have expressed during their life an objection to organ donation because of their philosophical or religious beliefs. Despite this, the relatives are always asked to confirm that the deceased did not oppose donation. This evinces respect for the family, something that Greeks expect.

Currently some Greek patients go abroad to receive heart or liver transplants; they have contacted the Hellenic Transplant Service to enquire whether we can procure organs for these operations. We do not know whether donors will equal or exceed supply, as we have no data on the likely demand.

Nevertheless, the Hellenic Transplant Service has begun an intensive effort in the intensive care units to increase the number of potential donors. A team of doctors and coordinators has visited all units and discussed with doctors and nurses such estimates of need as are available, explained the role of coordinators and supplied them with forms on which to report all potential donors. Every week the coordinators visit the intensive care units to discuss possible problems with the appointed contact person. Directors of these units have been begun to organise discussion meetings with all hospital staff. A one-day course for ICU staff, on a potential donors' protocol, has been organised.

At the same time the Hellenic Transplant Service has put its major effort into heightening awareness of organ donation in the general public. We have circulated informative material widely, in the form of leaflets, stickers and a poster on vehicles, banks, public services, and hospitals. A short message has been written on telephone and electricity bills and at certain times a similar message is stamped on all mail.

Many public talks have been held in several cities and towns of Greece in collaboration with local authorities, and about 15 private associations collaborate with YSE for promoting the idea of organ donation.

Recently the Service has started a new, dynamic campaign to promote kidney and cornea donation involving distribution of new informative leaflets throughout the country, a message to be given via all radio stations

and a similar message prepared for television. We are also negotiating the making of a film on the subject for a family TV programme. Although most kidney donation is from living donors, the idea that kidneys, and therefore also hearts or livers, may be obtained for transplantation from cadavers is taking hold through these messages.

The Euro video film on transplantation has been translated into Greek for presentation on TV prior to a discussion in which members of scientific societies will discuss medical, medicolegal, legal, ethical and religious aspects of transplantation. We have also produced 40 copies of this film, to be given to the army for showing on special Army educational programmes, and sponsored a pan-Hellenic competition for an artistic poster on the subject of organ donation.

These efforts have been greatly assisted by G Kastrinakis, a reporter with kidney failure unsuccessfully transplanted from his mother. He is trying to promote organ donation. His book on the subject is in its 4th edition and is distributed free. In collaboration with the Ministry of Youth, articles have been produced for the magazine for young people sensitising them to organ donation.

Beginning heart and liver transplantation

Medical teams will have to decide to begin and be ready to face success and failure. All doctors (physicians, hepatologists, cardiologists, surgeons) must be made aware of the potential of heart and liver transplantation in Greece and specific waiting lists must be formed. When this is done the search for transplantable organs can begin.

If, when the process begins, transplantation of cadaveric kidneys or corneas is still low in Greece, the existence of the EC should help Greek patients through supply of organs by other EC countries. Greece could reciprocate by supplying organs suitable for transplantation but which there are no facilities to transplant them yet in Greece or for which no suitable recipients have been found.

Appendix 1: Data on kidney and cornea donation

In 1985 the Hellenic Transplant Service (YSE) initiated a system of written declarations of willingness to donate and the 'donor card' was established.

Number of donors: Dec 1986 17,000; Dec 1988 30,000; Dec 1989 36,000.
Age: most donors are between 20 and 40 years old.
Willingness to donate: kidneys 32 per cent; eyes 31.6 per cent; other organ 24.3 per cent; whole body 11 per cent.

Appendix 2: Donated organs used in Athens, June 1985–December 1989

	No. of cases reported					Organs not used	Reasons why organs not used
	1985	1986	1987	1988	1989		
Kidney donors	6	27	29	31	39	80%	Medical 84% No permission 15% Medicolegal 1%
(total)			132				
Cornea donors	11	14	52	64	62	46%	Medical 55% No permission 26% Medicolegal 14% Organisational 5%
(total)			203				
Multi-organ donors	–	–	–	1	6	60%	Medical reasons
(total)			7				

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).

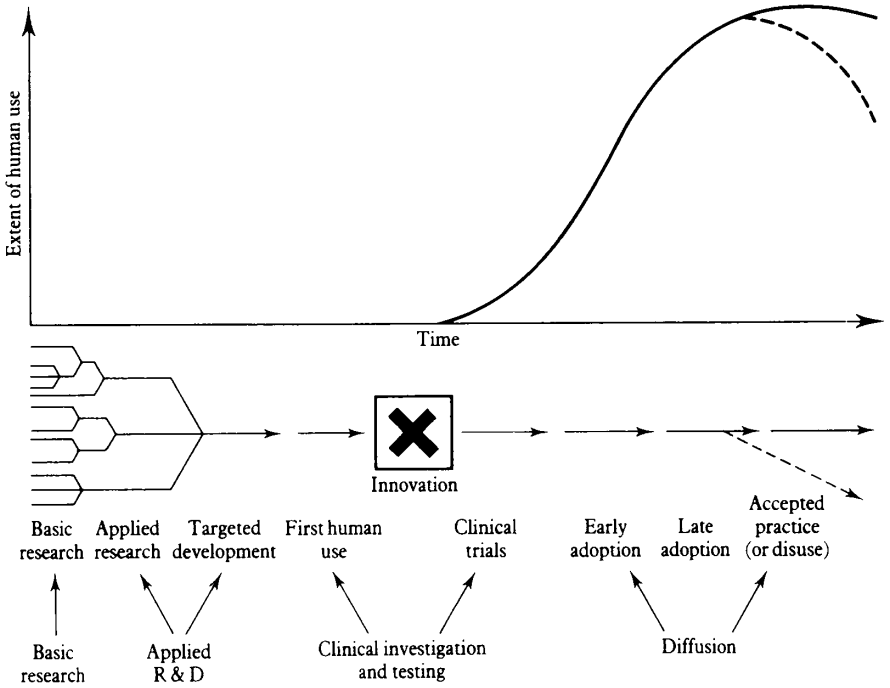
In this overview the introduction and diffusion of the three technologies are examined and then the factors which influenced the speed and extent of this diffusion – this includes the nature of the technologies themselves, social and economic characteristics of the countries, and finally the more specific 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-
Ireland – no organised screening programme				Italy	mation
Luxembourg – none undertaken within country, counselling and screening tests referred to other countries.				France – no national programme but some undertaken	

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

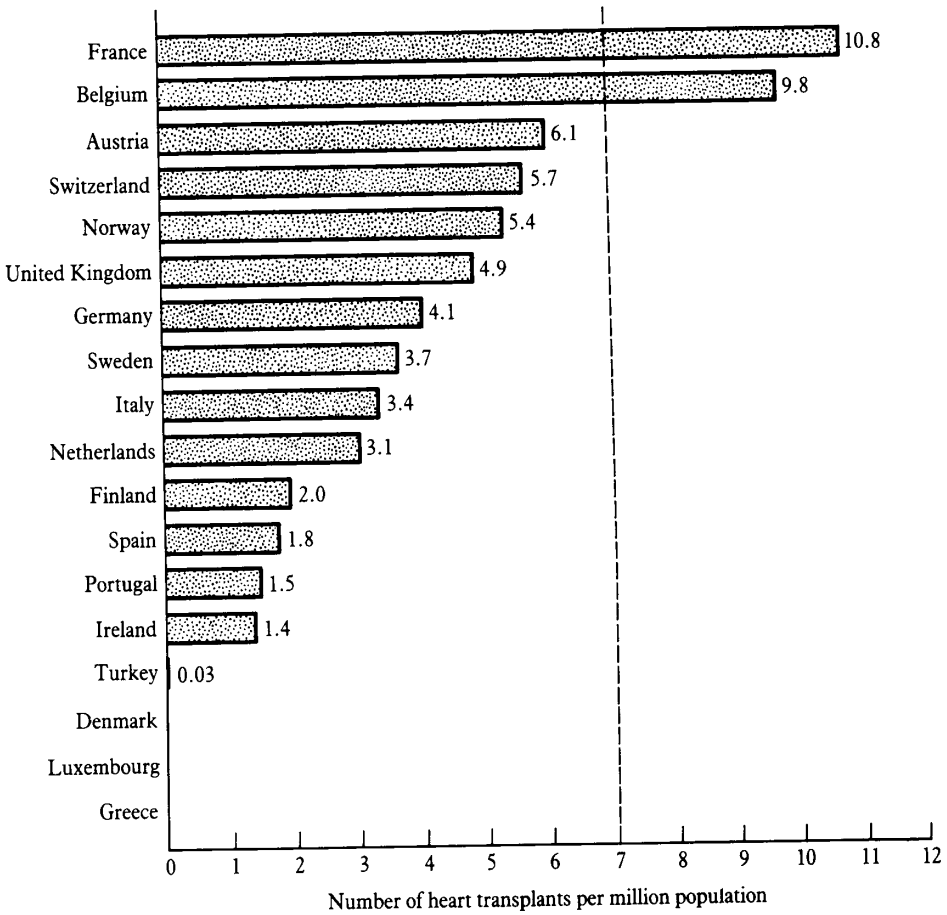
Country	Year
UK	1969
Denmark	1970
FRG	1970
Netherlands	1970
Spain	1970
Belgium	1972
Portugal	1972
France	1973
Italy	1975
Greece	1976
Sweden	1970–71

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)

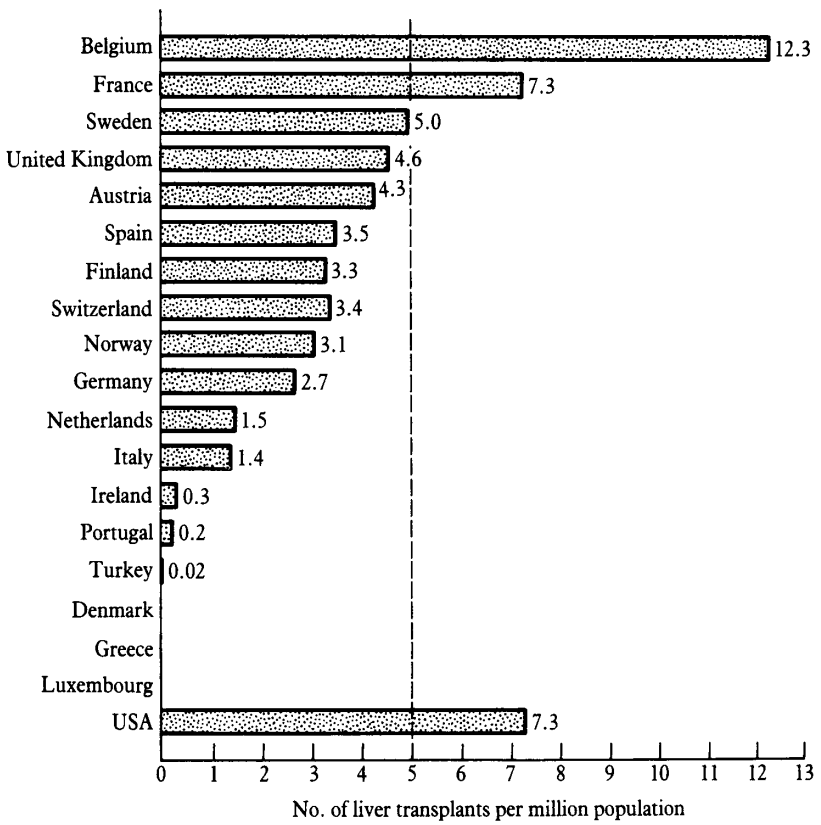


countries have been more influenced by the Catholic Church. As always, there are exceptions to the rule. While Belgium had until very recently very restrictive abortion laws this did not stop prenatal screening (nor, it seems, abortion of defective fetuses) from taking place.

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.

REFERENCES

1. Stocking B. Expensive health technologies. Oxford University Press, Oxford, 1988.

2. Rogers E M. Diffusion of innovations. 3rd Edition. New York Free Press, New York, 1980.

3. Aaron H and Swartz W. The painful prescription: retaining hospital care. The Brookings Institution, Washington DC, 1984.

4. Halper T. The misfortunes of others: end stage renal disease in the United Kingdom. Cambridge University Press, Cambridge, England, 1989.

5. Buxton M J *et al.* Heart transplantation in the UK. *In* Expensive health technologies. Oxford University Press, Oxford, 1988, pp 36–48.

6. Stocking B. Initiative and inertia. Nuffield Provincial Hospitals Trust, London, 1985.

7. Office of Technology Assessment. The impact of randomised clinical trials on health policy and medical practice. US Congress, Washington DC, 1983.

8. Steering Committee on Future Health Scenarios. Anticipating and assessing health care technology. Martinus Nijhoff, Dordrecht, 1987.

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; 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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