Medicine and Management

Proceedings of the fifth Trent Region Seminar
on Health Service Developments in the Decade Ahead
held in Sheffield, 25–26 June 1987

Imaging

Mammography, MR and CT Scanning, Ultrasound

Stereotactic Radiosurgery

Childhood Leukaemia

Osseointegrated Dental Implants

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FOREWORD

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Chairman,
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These Seminars are designed to encourage clinicians and scientists to acquaint Health Authority members and managers with recent and likely future developments, and to promote discussion about the strategic implications and their costs, and the degree of organisational change that is necessary for their implementation.

A special feature of this Seminar was its attempt to look at one of the most fast-moving areas of technological innovation. As an engineer, I can share in the excitement engendered by the rapid and impressive improvements in visual imaging techniques to be described by the radiologists. On the other hand, when I look at it from the manager's standpoint, I wonder whether such costly precision is essential when there are still so many other unmet demands for much more basic forms of care. I am sure that we need both, but we must weigh our priorities very carefully. Another reason why this Seminar is special is that we have chosen to include contributions on stereotactic radiosurgery and osseointegrated dental implants because they are highly significant innovations when viewed from the national perspective. Both will attract much attention for that reason alone. Lastly, childhood leukaemia is important because, I am told, it is the commonest of all malignancies in children and has caused so much family distress. I believe that the much improved outlook at least in one type of acute leukaemia owes a great deal to ensuring that, for the time being at least, the care of those with uncommon disorders is concentrated in the hands of the specialists.

It would be very remiss of me not to thank the contributors. It is asking a lot to take doctors away from their clinical duties, but I feel that it is very important for managers, clinicians and members to sit down and discuss topics outside their spheres

of interest. I must also pay tribute to Professor Scott for setting up this series of Seminars. It is extremely valuable for health care policies to be discussed in such a forum and helps us greatly in determining our priorities between competing demands for development.

MICHAEL CARLISLE

PREFACE

It is difficult for anyone, including those with medical qualifications, to keep up to date with recent advances in medicine, especially with the highly technical procedures based on new scientific discoveries which are now being used in diagnosis and treatment. The papers which follow are based on the contributions to the fifth of the Trent Region Seminars which were initiated by Professor J A Scott when he was Regional Medical Officer. They have enabled leaders at various growing points in medicine to describe to health service managers recent discoveries, to indicate their importance and to forecast their future demands on health service resources.

In addition to managers from the Region, consultants in the specialties concerned were invited to ensure a wide range of opinion on the importance or otherwise of the advances under discussion.

The introduction of managers into the National Health Service has taken place in a period of great financial stringency which coincides with some remarkable advances in diagnosis and treatment. With the current rigorous limitation on expenditure it is more important than ever to ensure that financial and staff resources are directed to parts of the health service which will bring most benefit to patients.

Managers as well as clinicians need to be able to evaluate the advances that are taking place in order to advise on the most efficient use of health service resources. Clinicians and medical scientists can promote this understanding by describing the advances as far as possible in non-technical terms. This the contributors have tried to do. We believe that the topics chosen for discussion will be of interest to managers and to clinicians in the subjects concerned and also to others working in related branches of medicine.

Mrs Margaret Riley and Mrs Susan Gray prepared the papers for publication and Mr Bernard Crossland has again

been responsible for the design and technical aspects of production. The Nuffield Provincial Hospitals Trust has funded, marketed and distributed the reports. I am grateful to Dr Paul Snell, who has edited the previous reports in this series, for his helpful advice in the editing of this the fifth report. The Trent seminars continue and further reports will appear in due course.

JOHN PEMBERTON

September 1988

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MAMMOGRAPHY IN THE DECADE AHEAD

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INTRODUCTION BY DR D C JAMES

We can look forward to the next decade as an exciting and challenging time. Most of the developments that have taken place have been in the new imaging techniques of ultrasound, tomography and magnetic resonance. All these have come about because of changes in technology and the great advances that have been made in the manufacturing industry. Much of the pioneering work in this field has been done in this country, but as with all high technology medicine it is not cheap. It is up to us as radiologists to see that these resources are used effectively and efficiently. Perhaps our most difficult task is getting the message across to our colleagues, some of whom may think why should they ask for one investigation when they can ask for a half-a-dozen. We have to persuade them to ask for the most useful investigation in any given circumstances.

DR ROEBUCK

The gold standard of breast imaging at the present time is X-ray mammography. Film/Screen techniques and Xerox are the two ways of producing the image. Film/Screen technology has made tremendous advances in the last few years and these are continuing. For example, the dose that is used during mammography is now less than 1/20 of that used in the famous New York trial of the early detection of cancer by mammography.

Xeromammography was a strong competitor to film mammography in the early days, but still requires the same high dose of irradiation and the images are, in the opinion of many, inferior to those obtained by modern films and screens and I think during the next decade we will see the end of xeromammography.

Ultrasound is an excellent second-line method of investigation to elucidate breast abnormalties. If the clinician who refers the patient has identified a problem which has not been elucidated on mammography, ultrasound should be used. Simple techniques with a hand-held linear array transducer but with high resolution are adequate. There will be more developments in this area during the decade ahead but more complex machines where the patient lies prone with the breasts in a water bath are unlikely to be developed in this country.

As far as breast imaging is concerned, magnetic resonance imaging (MRI) is of no practical value at the present time. The greatest potential for MRI in breast work is tissue characterisation and this may come. Considerable work is being undertaken in this area at the present time.

Thermography of the breast is a method which has virtually disappeared during the last decade. Other techniques which are being developed and which may become useful diagnostic tools during the next decade include transillumination with infra-red light, computed tomography, heavy-ion mammography and digital X-ray mammography. Alternatively, these may prove to have no practical value in the elucidation of breast disease.

There are two applications of mammography; the examination of patients with symptoms and the screening of well women. These are very different and should not be practised in the same location. They should, however, probably be practised by the same individuals. Those working in screening should also take part in the symptomatic service and *vice versa*. In screening there is a big boredom factor with great expectations of normality. In symptomatic work the prevalence of abnormal conditions is much higher. Screening, however, has no place in the radiology department and symptomatic work should not be done in a screening unit.

The presence of lumps or suspected lumps is the primary indication for mammography and the most feared symptom among women. Has mammography any role to play if a clinician finds a lump or a possible lump in the breast? I believe very definitely so. There is no place for mammography in the actual diagnosis of a lesion which is clinically detected and is highly suspicious of being cancer. This requires histology. The role of mammography is in situations where there is clinical doubt, then it may be possible to show the lesion is benign without operation, and thus reduce the number of benign biopsies. This is an application which will grow during the next decade.

If there is a clinically detectable cancer why do a mammogram at all? In the contralateral breast in the Nottingham series, three per cent of the individuals had mammographically detectable, clinically occult cancer at the time of the first presentation. It is very important for the management of the case that this second lesion is identified before treatment starts. This indication for mammography will undoubtedly become more widely appreciated in the next decade. It is, in addition, important to know the mammographic features of the original cancer. It is necessary to be able to tell the surgeon if it is likely to be removable, or if it is multi-focal or more extensive than it appears on palpation. If we know the mammographic features of the cancer we are more likely to be able to identify any residual tumour or recurrence after treatment. During follow-up of treated patients, particularly with breast conservation and radiotherapy, a form of management after treatment which will become widely employed, mammography is going to be very important to detect early recurrence.

By an assessment of the background pattern on a mammogram it is becoming possible to predict to some degree if a tumour is hormone dependent. In other words, is the woman going to benefit from hormone manipulation therapy? Eventually this may save the expense and delay entailed in obtaining oestrogen receptor assays on operative material. Pain and nipple discharge are other clinical indications for mammography which are traditionally considered less important than cancer but they are important in terms of disability. During the

next decade the use of mammography for patients with pain and discharge from the nipple is likely to increase.

In addition to changes in indications for mammography there are likely to be changes in sources of referral. Currently, virtually all referrals are by breast specialists. Considerable education is required before referrals should be accepted from a wider spectrum of doctors. It has to be ensured that individuals requesting the examination understand the limitations of that investigation as well as the value of it. If a patient has a clinical abnormality which seems to be of significance but a normal mammogram, the normality of the mammogram should be ignored in exactly the same way that if there is a mammographic abnormality, a negative clinical examination should be ignored. General practitioner access is a difficult problem and one which gives rise to considerable debate. It is difficult to see why general practitioners educated in the value and limitations of mammography should not have the same access to the service as similarly educated specialists.

There is going to be a great increase in mammographic screening. Two big questions which will require considerable research during the next decade are:

1 Is it possible to identify more accurately a target population or do we have to X-ray all women?

2 At what interval should women be screened?

Several characteristics help in the identification of high risk groups: older age groups, proven hyperplasia, a history of previous cancer and certain types of family history. There is some rather traumatic French work going on in which women are subjected to four quadrant histological examination in order to identify possible hyperplasia with atypia, or hyperplasia alone without atypia, thus defining various categories of risk group. It also seems possible that risk groups can be identified using infra-red transillumination.

Quality control in mammography is vitally important. It is essential to minimise both false positives and false negatives. False positives are important as a cause of unnecessary anxiety and result in unnecessary biopsies. False negatives are even more important. If a woman is wrongly reassured that she does not have cancer, then that lesion may not present until it has

grown beyond the curable stage. Quality control of film processing, the radiographers and their performance, the film readers and their performance and the radiologists and their performance are all equally important. It seems likely that this quality control and assessment of performance of staff will develop with screening.

There are other problems associated with screening which will require solving. Because of the way the funding is organised there has got to be some sharing of screening facilities between Health Districts. However, Districts like to be autonomous and there is going to be pressure to have screening set up in each District. It is likely that the target population will be increased to include younger women and also the screening interval may be decreased. It may well be that by introducing screening in each District, the facilities will be enlarged sufficiently to cope with this work. One major problem concerns the women outside the age group invited for screening. There is a need to establish a clear policy and promulgate this to general practitioners and the women involved. There is a tremendous educational requirement in this respect. The private sector will probably expand to offer a service to this age group, and it is important to ensure that this is in no way inferior to the service organised within the NHS.

Finally, a reference to what is likely to be the main thrust of research over the next decade:

1 The identification of high risk groups.

2 Tissue characterisation *in vivo*.

3 Computers for data storage and transmission and to assist with call and recall systems in screening programmes.

4 Computer assisted diagnosis.

These are some of the changes to be envisaged in the decade ahead.

DISCUSSION

The value of mobile mammography units was discussed. It was pointed out that these had the great advantage of making the service more accessible to women, particularly in rural areas, but it was not possible to process and read the films in the unit. This should be done in specialist centres.

The question of quality control in the private sector was discussed. Licensing was one possible method suggested for achieving acceptable standards. Highly trained staff from selected NHS centres should also be available to advise the private sector as well as other NHS centres.

The Nottingham centre is one of four national training centres for mammography and has also been asked to undertake quality control for the Trent Region. Dr Roebuck thought that every District General Hospital which has a breast surgeon and enough work to justify two breast clinics dealing with 50–100 cases a week should have a mammography unit. Radiologists reading the films should be trained in centres where many cases are screened and refresher courses should be available to them.

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MAGNETIC RESONANCE IMAGING: A CASE STUDY

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Great developments have been occurring in radiology in the last two decades, particularly in the field of new technology. We have witnessed the development of computed tomography, digital vascular imaging and latterly magnetic resonance imaging, which coupled with the introduction of safer contrast media have advanced the goal of obtaining more diagnostic information whilst reducing risk and discomfort for the patient.

Unfortunately, all of this new technology is complex and expensive, and inevitably, therefore, its availability is restricted. Furthermore the cost of these recent developments coupled with economic constraints has highlighted the need for such technology to be properly evaluated. This means a serious appraisal to determine which of their many potential applications can be said to result in proven benefit so that the indications for their use can be clearly defined. If one can identify groups of patients and the circumstances in which they can be expected to benefit, then this information can be used in deciding the scale of provision necessary to ensure that those patients who could benefit will have access to the techniques.

In the following case study I wish to consider three processes and the problems associated with them. The first process concerns the development of a new technology and here I would wish to stress the opportunities for collaboration between University Departments and NHS Departments. The second process concerns the evaluation of a new technology

which is a far more difficult task then appears at first sight, for as history shows, many technologies have been adopted only to be subsequently rejected when a fuller consideration showed them to be valueless. The final process concerns the proper utilisation of a new technology ensuring that its benefits are dispensed in the most effective fashion to the benefit of the community.

I shall be considering the latest technology to enter diagnostic radiology which is known as magnetic resonance imaging, a non-invasive method of imaging the body which completely avoids the use of ionising radiation. It uses instead radio waves in the presence of a carefully structured magnetic field to produce high quality cross-sectional images of the body that portray the constituent tissues. These images actually portray the distribution density of the hydrogen atoms contained in the water and fats of the body tissues. Images can be taken directly in any plane and at any point in the body.

Magnetic resonance has a singular advantage over other imaging techniques in that by changing the pattern of radio waves employed the contrast between the different tissues can be selectively altered and in this way different kinds of pathology can be highlighted. During a single examination, therefore, several sets of images can be generated, each contributing information of a different kind from which the final diagnosis is made.

The Development of Magnetic Resonance Imaging

Much of the early pioneer work in the development of magnetic resonance imaging (MRI) took place in Britain, principally in Aberdeen University, the Hammersmith Hospital and Nottingham University. Since July 1974 I have had the opportunity of collaborating with several talented physicists in exploring the potential of nuclear magnetic resonance (NMR) as the basis of an imaging method. The basic research demonstrated that NMR would indeed provide discrimination between different tissues and would allow one to identify flowing blood without the need for contrast agents (1). The multiplanar facility of MRI was demonstrated in Nottingham early in 1980 (2). In conjunction with the National Radiologi-

cal Protection Board and the DHSS, questions of hazard were addressed and guidelines on the use of the technique were issued.

The first clinical trial to document the demonstration of intra-cranial pathology was carried out on a resistive whole body prototype system in Nottingham (3). With support from GEC Medical a whole body system was built in the Queen's Medical Centre and with funding from the DHSS clinical trials were commenced. This scanner was replaced after 2 years by a Picker 0·15 Tesla resistive system.

The great interest generated in the early British results led to the construction of machines in several European and American centres. The time has now, however, long since passed when examinations were all carried out on laboratory prototypes. All the major X-ray manufacturing companies now offer at least one type of system and at the present time there are over 1000 MRI scanners installed world-wide with over 600 of these being in the USA. During the early stages of the development of MRI, exaggerated claims were made for its future in some sections of the press; on the other hand there were also those who urged caution suggesting we were witnessing the premature exploitation of an unproven technique. The truth lies at neither of these extremes; but it is clear that MRI has now become an accepted method of investigation.

The Clinical Evaluation of Magnetic Resonance Imaging

In our first clinical study we enumerated what we saw as the advantages of the method and which would be important in its subsequent utilisation. The fact that it avoided the use of ionising radiation and appeared to be unassociated with significant hazard would obviously be advantageous in paediatric applications and where several follow-up examinations were required. The ability to image in any plane made it easier to define the relationship of tumours for example to surrounding normal structures and facilitated assessment of tumour volumes as a prelude to radiation treatment. The lack of obtrusive artefacts from the base of the skull allowed one to obtain clearer pictures of basal structures. The ability to highlight blood flow without the need for intravenous

injections of contrast media and the ability to highlight different kinds of pathology by producing different types of images indicated that the technique would quickly become competitive with computed tomography.

As the number of patients examined increased anecdotal experience suggested the areas where application would be most fruitful. These include the brain and spinal cord; the musculoskeletal system and pelvis although the technique is also having a significant impact on the diagnosis of disease in other body systems. In addition the limitations of the method have also become apparent, some of which detract from its universal application. MRI results from a very weak interaction between radiofrequency radiation and the tissues of the body as a result of which it takes a relatively long time to collect sufficient data to reconstruct a cross-sectional image. Although several slices can be obtained simultaneously the patient is required to lie still during the period of data collection which is typically 5–20 minutes. In each examination several sets of images may be required and typically we allocate 45–60 minutes for a study. In order to obviate the blurring which involuntary body motions such as breathing would introduce complex gating procedures are necessary, although in the near future rapid imaging methods may remove the need for them and also reduce the requirements for anaesthesia in young children.

Comparative studies have been made with existing methods of examination in the same disorders to compare the diagnostic efficacy in terms of their relative abilities to disclose pathology. There is, however, a great need to carry out more prospective trials in order to determine how well MRI satisfies three criteria; the ability to detect patients who have disease, the ability to exclude those free of disease, and the gains to the individual and indeed to society as a whole as a result of making a diagnostic decision. The evaluation of the diagnostic process is very complex. The sensitivity, specificity and predictive capacity of the technique in a given context have to be assessed. Studies must take into account the experience of the observers and test the reproducibility of the results. The diagnosis in itself is not the final arbiter of utility, we need to determine whether making it alters management. It does not

of course always depend on the test result; it depends rather on the physician's response to the result of the test. There is no clear single end point to use in assessing the impact of a test result. In the long term we can look at whether use of a particular technology results in more cures or longer survival times. In the short term we could assess the impact on the number of invasive tests which have to be used to achieve a diagnosis, or the reduction in time of hospital stay. The avoidance of fruitless surgery and exclusion of disease are difficult to quantify but very real benefits nonetheless.

Given our current state of knowledge we might ask whether any such benefits are already identifiable from the use of MRI. I have chosen three examples from our own experience; in the first we have shown that MRI can lead to a reduction in the use of invasive tests and *pari passu* a decreased need for admission to hospital; in the second the early detection and localisation of disease allows a more precise application of appropriate therapy without delay; and finally in the third we have shown how MRI can replace a series of alternative radiological tests saving both time and money.

(a) Disc disease

Disorders of the lower back are common and result in many attendances at GP and specialist clinics. They represent a very important cause of loss of time from work with attendant consequences for the economy.

Derangement of an intervertebral disc is a frequent cause of the patient's disability. An invasive procedure, myelography, is normally used to demonstrate a protrusion of a disc. In order to demonstrate whether a disc has degenerated, which is an essential prelude to certain operative treatments, it has been necessary to insert a needle into the disc under local anaesthetic and inject contrast medium, a procedure known as discography. Both procedures are time-consuming and require admission to hospital. We were the first to demonstrate in 1981 that with MRI the internal structure of the disc could be demonstrated (4). Both disc protrusions and disc degeneration can be identified and we believe that eventually many myelograms and discograms will be eliminated (*figure 2.1*). In Nottingham over 100 patients each year have in the past been

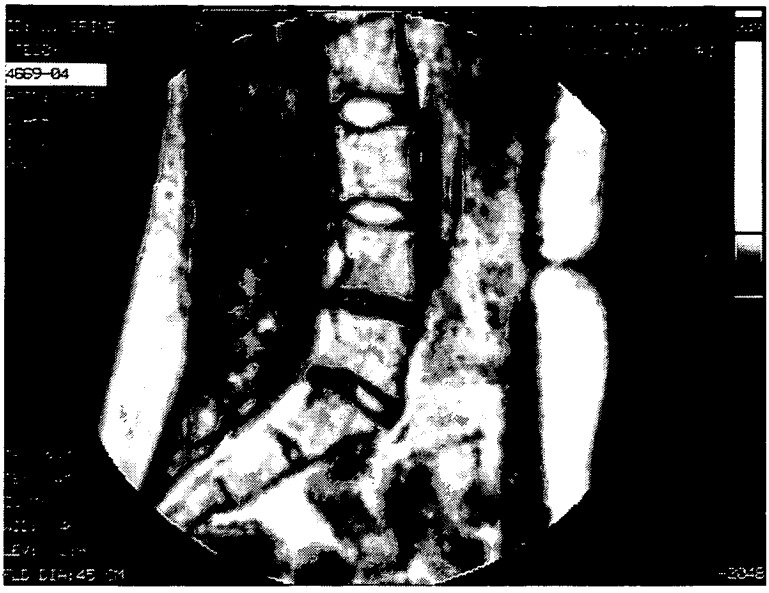

FIG. 2.1. Midline sagittal scan of the lumbar spine. The discs in the upper spine are normal and have a white central region or nucleus with a black rim. The lower two discs show narrowing and evidence of degeneration with partial loss of the central nucleus. In addition each disc is seen to be protruding backwards into the spinal canal.

examined by discography; since the early advent of magnetic resonance this number has fallen by half.

(*b*) *Tumour staging*

Carcinoma of the cervix is the second most common gynaecological cancer. The prognosis is determined by the stage of disease at the time of diagnosis with a 50 per cent five-year survival rate in those with invasive disease. Accurate staging at presentation is therefore important in order to assess prognosis and to choose the appropriate treatment. There is an inaccuracy in clinical staging and in five papers selected from the literature the overall figure was some 34 per cent. Imaging techniques such as computerised tomography (CT), whilst of value in advanced disease, have had little to offer in early disease. With MRI we have shown that a clear depiction of disease can be achieved (*5*) (*figure 2.2*). This information can

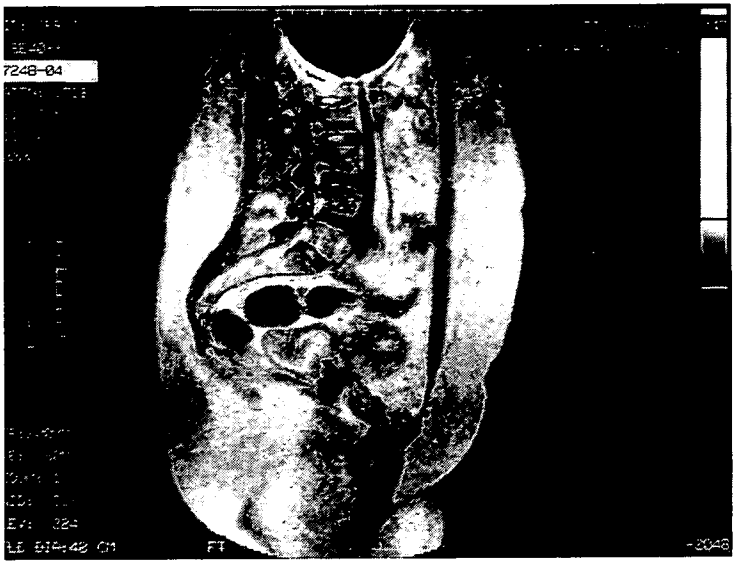

FIG. 2.2. Midline sagittal scan of the pelvis in a patient with carcinoma of the cervix.

be used to separate those patients where a total surgical extirpation can be achieved from those where the extent of spread indicates that treatment with radiotherapy is appropriate. In the latter group of patients a fruitless laparotomy is thus avoided.

It has also now been convincingly demonstrated that MRI is superior to all other methods in assessing the extension of bone tumours both inside and outside the parent bone (6). This is important today when greater efforts are made to avoid amputation and carry out salvage operations where the tumour is excised and replaced by a prosthesis.

(*c*) *Evaluation of the cranio-vertebral junction*

The junctional zone between the head and the spine is referred to as the cranio-vertebral junction. Many types of pathology occur at this level and unfortunately on clinical presentation it is seldom possible to distinguish between them. It is however vital to separate operable tumours and other lesions which

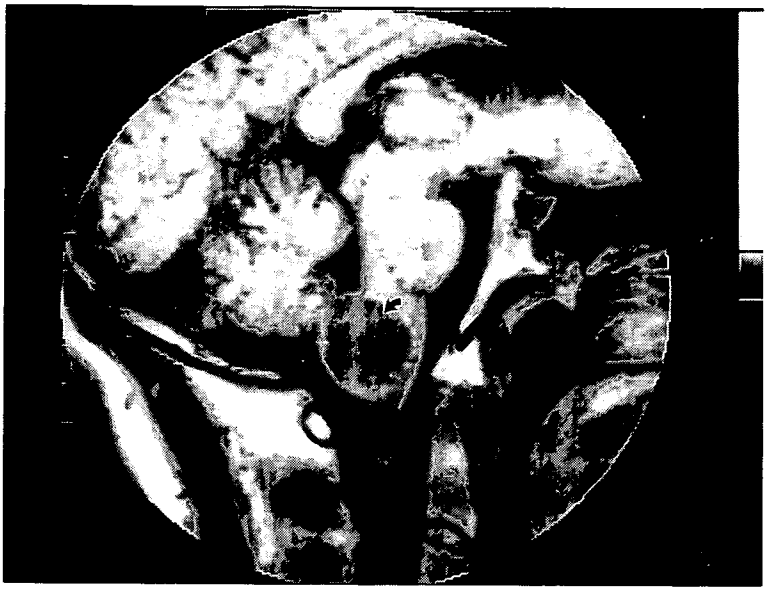

FIG. 2.3. Midline sagittal scan of the cranio-vertebral junction in a patient with a cystic tumour (arrowed) which was not disclosed on CT.

require other forms of treatment. Radiological evaluation of this region has always been difficult and frequently several tests have been required to clarify the relevant anatomy. In 1983 we suggested that the assessment of clinical problems involving this region would be simplified by the advent of MRI and lead to a decline in the use of invasive procedures (7). Today it is accepted that MRI is the method of choice in the examination of this region (*figure 2.3*).

Research Applications of MRI

It has become apparent that MRI is a valuable research tool for addressing fundamental questions relating to the pathophysiology, the natural history and effects of potential therapies in conditions such as multiple sclerosis and head injuries. In our own unit we have been studying the incidence of degenerative discs in a population who have no back disorder but who were scanned for some other reason.

We have found that the number of subjects with one or

more degenerative discs rises linearly with age (8). This information was not previously available but it is essential to have if we are to properly evaluate the findings in those with back problems and determine whether degeneration is a risk factor for developing the potentially serious problem of disc prolapse.

Utilisation of MRI

Once a new imaging technology is made available it is essential to ensure that it is used appropriately. Consideration requires to be given to ensuring that clinical colleagues are given sufficient information which will allow them to integrate the method into their repertoire of imaging requests. Furthermore, teaching programmes for students and junior doctors need to emphasise the constant challenge facing clinicians and radiologists of how clinical knowledge and skills are best complemented by the application of radiological tests in the goal of reducing diagnostic uncertainty.

Concluding Remarks

The central theme of this case study has been the need for proper evaluation of imaging techniques: one can argue that there is little use in improving the management of health care and its more efficient delivery unless one also ensures that the practices employed result in improved outcome for the patients.

The use of audit procedures and performance indicators for clinical activities must be done with care. In an X-ray department the resource inputs, that is the staff, the plant and the consumables, can all be costed. Certain outputs can also be measured, for example the number of patients examined, the number of procedures carried out, the intensity of utilisation of plant and rooms. We need to be assured, however, the best outcome is associated with a given output and that the activity of a Department is directed towards achieving the best outcome. These limitations of conventional performance indicators simply reflect that quantity of care does not always equate with quality of care. One could argue a good case for there being some central body concerned with overseeing the assessment of new technology. Furthermore,

the NHS requires to have some mechanism to ensure that the diffusion of new technology runs parallel with, and not ahead of, the degree of proven benefit. Given the very high cost of modern imaging equipment such as MRI it is relevant to ask whether the appropriate level of a technology and its deployment ought not be decided centrally and funded out of earmarked resources. Finally, whilst academic Departments of Radiology clearly have a duty to ensure the proper dissemination of knowledge about the appropriate use of tests, I believe they could also be given a greater role in the evaluation of new technologies; because, within the University setting it is possible to assemble the multidisciplinary team essential for such a task.

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DISCUSSION

The main discussion centred around the cost of MRI; the likely developments in the future; the extent to which it might replace CT and where, on our current knowledge of proven applications, the scanners should be sited.

Scanners range in price from approximately £0·5–1·5m, the cost depends largely on the operational field strength and type of magnet used. The optimum field strength for imaging is probably about 0·5 Tesla but excellent results can be obtained at lower fields with consequent cost saving. The impetus to develop very high field systems has been the requirement to assess the value of MR spectroscopy but this is unlikely to be a clinical tool for many years and at present is largely used for fundamental research into tissue metabolism. There is a need for a cheaper low field system and this will probably emerge in the near future. So far as the Nottingham system is concerned this is a low field resistive system operating at 0·15 Tesla. The total revenue cost *per annum* when running as a research unit was £142,000 of which £55,000 was for the service contract. The scanner operates for an eight-hour day and just over 2,000 scans were carried out during 1986. MRI is a relatively slow procedure and this limits throughput and also means that involuntary body movements such as breathing introduce blurring into the images. Professor Mansfield has pioneered a technique in Nottingham for speeding up imaging which actually allows pictures to be taken in real time. Although there are limitations at present in the level of detail which can be identified by this method, there is every expectation of considerable improvement in the near future. There have been other developments in the software and hardware in the last few years which have led to greatly improved image quality. The principal beneficiary of MRI has been neuroscience and a strong case can be made for all Regional centres of neurosurgery, if not having a system of their own, at least having access to one. A case is growing for its use in orthopaedics and pelvic disease and it will in time make a significant impact on the management of patients with disease in other systems.

It is unlikely even in its neurological applications that MRI will completely replace CT for the present. Duration of examination precludes its use in the very sick patient, for example after head injury. Furthermore, there are groups of patients who have to be excluded, such as those who have certain occlusive vascular clips *in situ*, those with cardiac pacemakers, and women in early pregnancy. As scanning speeds increase and become competitive with those of CT, a change in the balance between the number of the two types of scanner may be expected.

It was noted in the discussion that MRI had been used in a study of the spines of apparently normal people. A large proportion of those over 70 were found to have degeneration of the intervertebral discs although they did not complain of back pain. It is important therefore not to assume that a patient's back pain is necessarily due to degeneration of the disc revealed by MRI.

MRI scanners have been introduced in the USA on a much wider scale than in the UK. There are more than 650 in the USA compared with about 20 in the UK, about 200 in Japan and about 200 in West Germany. There are only two in the Trent Region, one for research and one for clinical work.

High field strength scanners are much more expensive than low field scanners and produce better quality images but low field scanners also give satisfactory clinical results without some of the disadvantages of high field scanners.

The high cost of servicing the Nottingham machine, £50,000 *per annum*, was commented upon and it was asked whether this was a reasonable charge, particularly in view of the reliability of the scanner and the infrequency of mechanical breakdown.

3

COMPUTERISED TOMOGRAPHY (CT) SCANNING

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Principles of CT Scanning

Computerised tomography was first introduced in 1972. X-ray slices are taken through the body rather like taking slices out of a loaf of bread to see the interior. This is achieved by a rotating X-ray tube which emits a collimated (*i.e.* a 'thin sheet') beam of X-rays which passes through the patient. This transmitted beam is then converted into an electrical signal by detectors positioned opposite the X-ray tube. The electrical signals are stored in a computer.

After the X-ray tube has rotated around the patient (the time taken for this is called the 'scan time'), all the stored electrical signals are processed by the computer to determine how much of the X-ray beam has been absorbed in each of a pre-determined matrix of squares. The amount of absorption in each square is represented by a number. Hence it is a digital image. The higher the number, the denser the material (more X-rays have been absorbed). A grey scale is assigned so that high densities (*e.g.* bone) are displayed as white; intermediate densities (*e.g.* soft tissues) are displayed as varying shades of grey; low densities (*e.g.* air) are displayed as black. The time taken for the image to be processed by the computer is called the 'reconstruction time'.

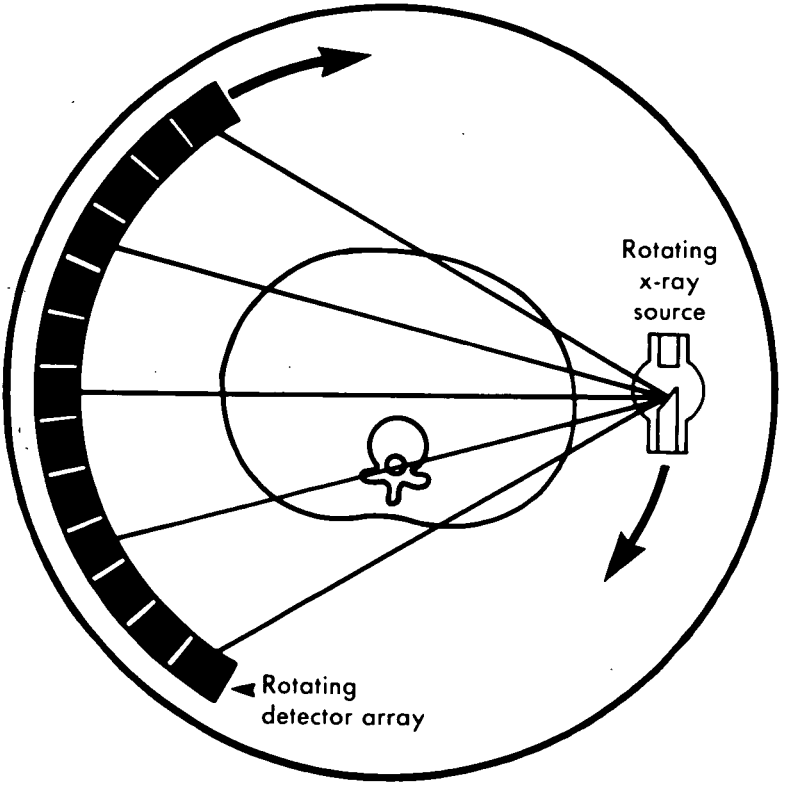
The table on which the patient lies moves to a new position and another X-ray 'slice' is taken through the patient. Although modern scanners can indeed scan the whole body, in practice this would take a long time so scans are usually localised to the particular region of clinical interest.

Technical Development

(*a*) *Third and fourth generation scanners*

Prototype scanners were produced by EMI in the early 1970s, but there was a rapid development of hardware and software over the ensuing years, predominantly by American, Dutch, German and Japanese firms. This has led to the so-called third and fourth generation scanners which have been available since the late 1970s and early 1980s. The term 'fourth generation' does not necessarily imply superiority to 'third generation'. Each type has its advantages and disadvantages.

FIG. 3.1. Diagram of CT scanner in which tube and detectors rotate.

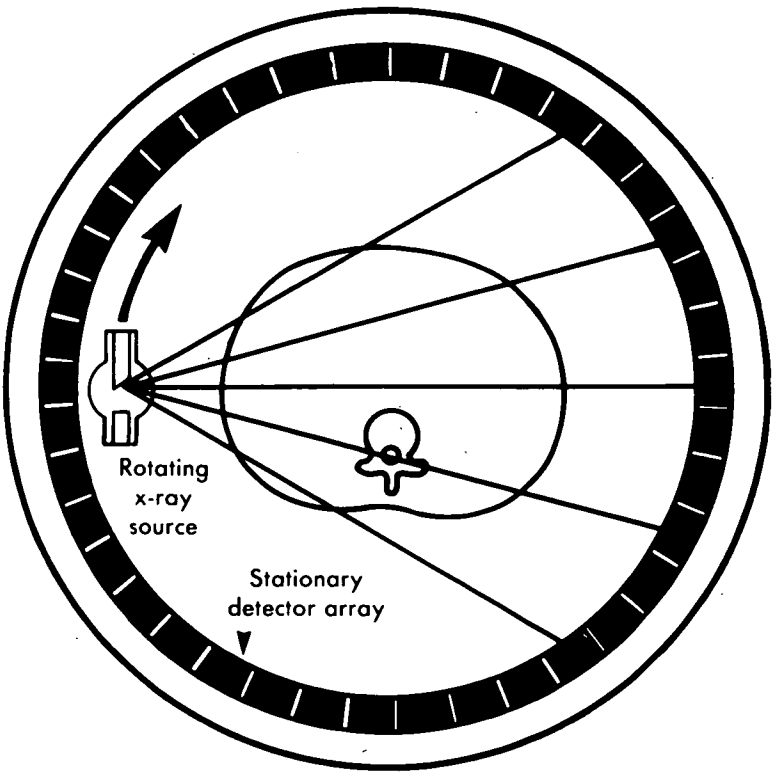


Rotate-only scanner.

In the third generation (*figure 3.1*) the tube and detectors rotate. The contrast resolution is slightly better due to the geometry of the detectors which produce less 'noise'.

In the fourth generation (*figure 3.2*) only the tube rotates. 'Noise' due to scatter has to be compensated for by grids which slightly increases the dose of X-rays required. The spatial resolution is slightly better due to the geometry of the detectors which produces multiple overlaps and therefore improves the accuracy of the computer processing.

FIG. 3.2. Diagram of CT scanner in which only the tube rotates.



Rotate scanner with stationary detectors.

(*b*) *General improvements*

Hardware

(i) Gantry aperture: increased to 60–70 cms which allows all modern scanners to be used as general purpose machines (*i.e.* brain and body scanners).

(ii) Gantry tilt: the gantry can be tilted 20–25° so that direct coronal scans of the pituitary fossa can be performed. It also enables scans of the lumbar spine to be performed parallel to most intervertebral discs.

(iii) Faster scan time: now 1–5 seconds.

Software

(i) Scanogram, pilot or scout (these are equivalent terms): the ability to take a digital X-ray image prior to scanning allows precise positioning for scanning.

(ii) Faster reconstruction time: now 5–25 seconds.

(iii) Image manipulation: images can be reformed in the optimal plane to study the lesion. They can also be 'zoomed' to magnify the image and increase spatial resolution.

Recent Technical Advances

The rapid development of CT scanner hardware and software that occurred in the late 1970s and early 1980s has now slowed down. The only major new technical development is the Imatron scanner which can perform 17 slices per second and so has the facility for cine-CT. However it is expensive and its main application would be specialised cardiac work where it would compare unfavourably with magnetic resonance imaging (MRI).

Several useful upgrading elements have come on to the market recently. Optical discs can store about three months of body scan images on a single disc with virtually instantaneous access. However tapes, although cumbersome, are far less expensive. Laser imagers allow the 'hard copy' (*i.e.* film record of the monitor image) to have the same resolution as the monitor image. Perhaps more importantly they record images

in a fraction of the time required by the standard 'hard copy' imagers. Unfortunately they are also about four times more expensive—approximately £40,000.

Software packages that have recently become available include 3-D imaging (which is proving particularly useful in the assessment and management of complex facial, spinal, pelvic and shoulder girdle fractures) and bone mineral quantification (with important applications in assessing the management of osteoporosis in middle-aged women).

Clinical Applications

There are now far too many clinical applications to be listed individually and only major applications will be outlined. It is important to realise that in many cases it is still essential to 'work-up' a patient with the simpler, cheaper and more easily available investigations, such as ultrasound, before resorting to a CT scan. In general it should be viewed more as a non-invasive technique for resolving diagnostic problems and so, apart from the old standard tomographic unit, it cannot be viewed as a replacement for other types of imaging equipment. It has however replaced certain radiographic procedures. For example, the number of lymphangiograms performed to stage malignancies has fallen dramatically since the advent of CT scanning. The number of myelograms for sciatica could also be reduced if there were sufficient CT capacity to accommodate these patients.

Brain: CT is at present the standard method of assessing intracranial pathology. The role of MRI is discussed later.

Oncology: this accounts for at least 40 per cent of the workload of a body scanner serving a District with an oncology/radiotherapy centre. The bulk of cases are lymphomas and testicular tumours. CT is used in diagnosis, staging, planning and follow-up of cancer patients. The bulk of paediatric work falls into this category.

Cardiothoracic: the major role is to assess mediastinal masses, detect suspected bronchial carcinomas and assess known

bronchial carcinomas for curative treatment. It is also very useful in assessing pleural disease and bronchiectasis.

Abdomen: CT is by far the best technique for visualising retroperitoneal pathology. It is used particularly for assessing the pancreas (*e.g.* complications of pancreatitis, operability of pancreatic carcinomas). Adrenal pathology is best studied by CT as it is virtually impossible to image satisfactorily by other techniques. Any intra-abdominal mass of indeterminate origin should be assessed by CT to facilitate surgical planning. The search for occult malignancy and abscesses in patients with pyrexia of unknown origin is best performed by CT.

Musculoskeletal: CT is a good non-invasive way of investigating low back pain and sciatica on an outpatient basis (myelography is invasive and requires admission overnight). Due to the large numbers involved, CT should only be performed if surgery is being considered. CT is also invaluable in investigating spinal and pelvic trauma, and the nature and extent of soft tissue masses.

Head and neck: CT is essential for assessing masses in this region. Pathology of the skull base, middle ear, nasopharynx and larynx are best investigated by this method.

TABLE 3.1. *Typical Number of Scans per Month for a Teaching Hospital Body Scanner*

	Number	%
Brain	45	15
Head and neck	15	5
Chest	41	14
Abdomen	80	27
Chest and abdomen	70	24
Spine	33	11
Orthopaedic	10	3
Interventional	4	1
Total	298	100

Interventional: masses can be accurately biopsied under CT guidance to obtain a tissue diagnosis. Although the number of cases is small, this is an extremely important aspect of CT work. Certain types of abscesses can also be drained under CT control, thus avoiding surgery.

A rough guide to the number and type of scans performed on a teaching hospital body scanner (with an associated oncology unit) in a typical month is shown in *table 3.1.*

Limitations

(*a*) *Technical*

Beam hardening. Low energy photons in the X-ray beam are absorbed by high density structures such as the petrous ridge in the skull, leaving only high energy photons in the beam. These are more penetrating and therefore cause a low density artefact. This is a particular problem in the posterior cranial fossa and cervico-thoracic junction.

High density material. The presence of extremely high density material such as barium, metal hip prostheses and teeth fillings in the region scanned causes an 'over-ranging' computer artefact. This manifests itself as a 'star burst' pattern.

Resolution. No imaging method is perfect. The limit of spatial resolution of a lesion which has a density close to that of soft tissue is 5mm–1cm. Small infiltrative lesions can be missed if their density is close to that of normal tissue.

Partial volume. The standard slice thickness is 10mm for body scans. Abnormalities smaller than this will mean that normal tissue will also be included in the slice and the computer will given an 'average' reading for density.

Movement. No matter how good the potential of an imaging system, if the patient is restless due to pain, breathlessness or confusion, and cannot lie still, the images will be severely degraded.

(*b*) *Medical*

Tissue specificity. CT, although good at detecting abnormal tissue, is not tissue specific (*i.e.* tumour, abscess and haematoma can all look identical in certain circumstances) and so correlation with clinical findings is still very important. However, CT guided biopsy is very useful to help differentiate between these conditions.

Gastro-intestinal tract. Lesions within the lumen of the gastro-intestinal tract are poorly evaluated by CT due to artefacts such as food residue. Barium studies and endoscopy remain the standard investigations. The biliary tract is poorly imaged by CT and ultrasound remains the standard investigation.

Cardiac imaging. This is difficult due to cardiac motion. Gated scans can be performed but these are complex.

Diaphragm. Lesions involving the diaphragm are well visualised by CT. However, it may be difficult to assess whether they have penetrated through the diaphragm (with obvious surgical implications) due to the fact that the transverse slices are parallel to the diaphragm and therefore image tissue partly above and partly below the diaphragm (partial volume effect).

(*c*) *Doses*

The surface dose varies widely due to different techniques used but lies in the range 1–7 cGy for most examinations, the highest dose being incurred in high resolution scanning of the lumbar spine.

Cost

All subsequent figures are approximate values and are only rough indicators.

(*a*) *Capital*

CT scanners vary in price from approximately £450,000 for a top of the range model to £200,000 (about the cost of a modern screening unit) for a new low-cost scanner recently released and aimed at District General Hospitals.

Installation costs must be added. This will depend on whether existing space can be used, but it is likely that building work will be required. It is essential that a scanner be sited as close as possible to the X-ray department to ensure its efficient use. It is of particular importance that adequate air conditioning for the scanner and computer is installed—if it is insufficient, endless problems with overheating may arise.

The working life of a scanner has been assessed as eight years by the Royal College of Radiologists. Accountants work on a 20 per cent *per annum* depreciation of capital value. In practice a scanner should have a working life of 12 to 15 years before it becomes uneconomical to replace parts.

(*b*) *Revenue*

Staff 1 Radiologist, 3 Radiographers, 1 Secretary, 1 Nurse, 1 Porter

To ensure an efficient throughput of patients, the above staffing level (whole time equivalent) is recommended for a high demand CT body scanner. A radiologist must be available for each session to ensure that the investigation is conducted so that the maximum information is gained. The radiographers are a vital element. It is complex work and to obtain a maximum throughput of patients it is essential that adequate senior radiographic staffing is allocated.

A new scanner generates a considerable amount of typing and clerical work which must be taken into account in staffing. The nurse and porter allocation, although advisable for a high throughput scanner, are less important than the other allocations.

Service contract. Although some scanners are worked without regular servicing in an attempt to save money, this is a less than satisfactory method of running a scanner. They are complex machines requiring regular maintenance to obtain the best results. If the scanner is predominantly involved in neurological work the scanner must have, in addition, emergency cover for breakdowns. Unfortunately, service contracts are expensive—about £40,000 *per annum.* It is possible that in the future global service contracts to cover several pieces of equipment may be negotiated with some advantage.

X-ray tube. Most firms guarantee a scanner tube on a pro-rata basis up to about 40,000 slices. In practice most tubes last for about 80,000 slices—just under a year for a busy X-ray department. The cost of a new tube for a top of the range scanner is approximately £20,000.

Consumables. The cost of items such as electricity, chemicals, contrast media and film will vary according to local practice, but could be between £10,000 and £15,000 per annum.

The overall running costs at present prices and based on the figures above will therefore be in the region of £150,000 to £160,000 *per annum.*

Throughput

This will depend on the type of workload. If this is mixed (*i.e.* brains and bodies), then the Royal College of Radiologists recommends a throughput of about 15 patients per day. This figure will rise to 22 to 25 per day for dedicated brain scanners. These figures will be affected adversely by inadequate staffing.

The provision of a Stand Alone Viewing Console (*i.e.* remote viewing console with dedicated computer) will increase the throughput in a busy department by allowing the radiologist to check images without holding up the scanning schedule. Out of hours working obviously helps to utilise the capital investment more efficiently, but patient compliance in attending for investigations in the evening would have to be evaluated.

Cost Benefit

One of the largest studies of the efficacy of CT (1), which reviewed the influence of CT in the management of 2,619 patients, came to the following conclusions:

50 per cent of scans provided a 'unique or substantial contribution to a diagnostic understanding'

15 per cent altered treatment

56 per cent increased the confidence of patient management by confirming the postulated clinical diagnosis

14 per cent led to a reduction in surgery

11 per cent led to a reduction in angiography.

With regard to the efficiency of CT, a typical study into the impact of CT on the investigation of abdominal masses (2) revealed that CT dramatically reduced the number of in-patient days needed to reach a diagnosis. If the cost of the in-patient bed was taken into account, then the mean cost of investigation of the CT group was less than half that of the group where standard imaging methods had been used. CT was also more accurate and as such can reduce the need for diagnostic laparotomies.

Availability

Because of the above studies and many more like them, CT has become an integral part of diagnostic 'work-up' in many clinical problems and the question is not whether we should have any, but how many should we have?

In 1979 a Royal College of Radiologists' Working Party recommended a provision of one scanner per 1·5 million of the population. However, due to the rapid development of CT technology that occurred subsequent to this report, this Working Party was reconvened in 1986 to reassess the situation. Their updated recommendation was that there should now be one scanner per 0·25 million of the population (3). This compares with one per 40,000 in Japan; one per 65,000 in the USA; one per 85,000 in West Germany; and one per 350,000 in Holland (4).

The Role of Magnetic Resonance Imaging

MRI is a major advance in imaging and has many inherent advantages over CT, particularly the marked superiority in contrast resolution (*i.e.* the ability to detect abnormal tissue), and direct multiplanar imaging facility with no loss of resolution. It has become of great importance for imaging the brain, spine, musculoskeletal abnormalities, and staging pelvic malignancies. It also has great potential for imaging the cardiovascular system. However at present it suffers from high cost, relatively low throughput (approximately 50 per cent of a CT scanner), and it has not yet been shown to be tissue specific. Also motion artefacts in the abdomen are still a problem unless sophisticated techniques are used.

The greater flexibility, reduced cost and faster throughput of CT scanning indicate that CT will remain the standard method of cross-sectional imaging. However MRI should be available in neurosurgical centres to help in those diagnostic problems unresolved by CT. The cost of MRI is unlikely to drop significantly in the foreseeable future and this, together with the need to concentrate expertise in this extremely complex imaging method, means that MRI will never become a District General Hospital facility.

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DISCUSSION

How many CT scanners are required and does each District General Hospital need to have one? Dr Nakielny thought that there should be one scanner per 250,000 population and that each major surgical and oncology centre should have one available. District General Hospitals with active departments of general and orthopaedic surgery should have one. The early scanners which could deal only with the brain have been largely discarded and have been replaced by much improved whole body scanners.

Although the cost of CT scanners had fallen to between £200,000 and £400,000, the price is unlikely to fall much lower.

Some concern was expressed that the replacements which would be required in the NHS, assuming one scanner per quarter of a million population, during the next ten years

might cost something like £8m per annum. Against the cost, however, must be set the savings resulting from investigating patients as outpatients instead of as inpatients. Another result of the use of the CT scanner is a reduction in the number of diagnostic laparotomies.

In discussing the running costs of CT it was noted that radiographers were needed because radiographic training was a legal requirement for anyone operating machines producing X-rays and also the operation of CT scanners was a highly technical procedure requiring anatomical as well as radiographic knowledge.

By the use of flexitime, the throughput of patients and therefore the cost-effectiveness, might be increased by operating the scanner in the evenings as well as in the daytime. However in one centre where this had been tried the attendance of patients had fallen off in the evenings but in another centre attendance was normal in the evenings. Staffing costs would increase and pilot studies should be carried out to study the cost-effectiveness of evening operation of the CT scanner.

Dr Nakielny referred to a recent cost-benefit study which demonstrated savings produced by the use of the CT scanner (1).

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4

ULTRASOUND SCANNING

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Introduction

Diagnostic ultrasound is probably the most important imaging modality developed in this century principally because of the concepts it has changed or introduced. One of the concepts it introduced was tissue characterisation (1). Ian Donald's work on identifying and characterising masses (2) in the human body using ultrasound was immediately recognised as an important advance. It is now a mature imaging technique.

Apparatus

Much of the early obstetric work was done using industrial flaw detectors. The first specialist machines were produced in the 1960s. A great variety of machines and scanning techniques have been produced since. The development of microelectronics during these years has resulted in significant advances in signal processing together with a relative fall in price so that machines cost much the same now as they did 15 years ago. There has always been a great variety of apparatus available and a number of options for each machine. This makes detailed comparison difficult and also means that different machines are much better adapted to different sorts of examinations and problems.

Current Status

Ultrasound is a general imaging technique that can be used to examine most parts of the body. It is blocked by gas or bone and this can limit its usefulness in a number of situations. The operator is always searching for a so-called acoustic window through which to direct the ultrasound beam to its target.

Ultrasound is reflected from interfaces in the body and the same probe acts as a transmitter and receiver. There is thus, quite apart from the difference in the type of radiation used (sound as opposed to ionising radiation), a fundamental difference from X-ray imaging. Unlike X-rays the beam of ultrasound degrades as it passes through tissues; thus it can only penetrate a certain distance into the body and this distance depends on the frequency. It produces slice-like images of the patient's body quite unlike the shadows cast by X-rays.

A number of early techniques have been discarded and a number of early descriptions of signs and theoretical analyses have also been discarded. One feature of current technique is that the operators are now describing signs which do not depend upon a theoretical interpretation, they are in fact making descriptions of what they see on the images and relating these directly to the anatomy and pathology.

Clinical Importance

Ultrasound is important because it provides images in situations where X-rays are either not useful or are inappropriate. It is harmless, painless, acceptable to the patient and can be used in any position of the patient and any orientation of the scan plane. It has revolutionised our knowledge of obstetrics and changed the practice of gynaecology. It provides information on cardiology which can be obtained in no other way and it has changed the management of jaundice, of neonatal intensive care and imaging practice in paediatrics has been transformed.

In cardiology ultrasound makes possible calculation of the speed of opening and closure of the valves of the heart and tumours of the heart can be detected. In the foetus and neonate the chambers of the heart can be counted and abnormal connections between them detected. In many situations it has replaced angiocardiography.

In obstetrics it is possible to detect foetal number, life and size from six weeks to term. Pregnancies both intra- and extra-uterine can now be detected at five weeks menstrual age by using intra-vaginal probes. Foetal abnormalities can be detected and foetal growth monitored. Serial studies of the

uterus and its contents have been of unique value in clarifying our knowledge of normal and complicated pregnancies.

In gynaecology the origin of pelvic masses can be detected and ovarian cancer can be detected by simple volumetric measurement at a stage when it is curable. The management of infertility relies heavily on ultrasound and much of current practice would not be possible without it.

The value of a different method of looking at the body is shown very well in the case of jaundice. It is important in jaundice to decide if there is a stone or some other obstruction in the bile ducts when an operation is necessary. If the jaundice is infective or has some other cause an operation can be lethal. Ultrasound accurately characterises patients into the two groups of obstructive and non-obstructive jaundice and in many cases provides good clues to the cause. Having categorised the patients it is then possible to go on to do other tests usually using X-rays to determine the level of obstruction. Thus X-ray imaging and ultrasound imaging are complementary both being general imaging techniques.

Costs

The costs and benefits of ultrasound can be compared in various ways and after the development of grey scale ultrasonography in about 1976 the resolution of ultrasound machines has often been compared with that of CT scanners. Sometimes ultrasound machines would be ahead and sometimes CT scanners. It is now clear that for spatial resolution and density discrimination with grey scale representation, computed tomography is better than ultrasound. However the capital costs are about ten times as great, say £500,000 compared with £50,000 for a good example of either machine and the revenue consequences are of the same order of difference £200,000 compared with £20,000 to run an ultrasound machine. The revenue consequences arise from the service contract for the CT scanner, the expense of replacing tubes, the cost of films and contrast medium. Staffing for a CT scanner is more expensive than for an ultrasound machine, typically three radiographers are required, one consultant radiologist and a clerk for the CT scanner whereas one clerk, one radiographer and a consultant would be a suitable

provision for an ultrasound machine and perhaps two could be operated by the same staff. The number of patients that can be examined on these machines in one year is about 2,500 for a CT scanner and about 4,500 patients for an ultrasound machine.

A Case Study

Another approach to costing examinations is to compare X-rays and ultrasound in their efficacy and their costs. A particularly informative example is the case of the detection of gall bladder disease. Ultrasound has revolutionised the management of jaundice and this is achieved by detecting dilated ducts in the liver. It can also detect gall stones, and it has therefore been said that this is all the physician really wants to know and that ultrasound should replace oral cholecystography. It is stated that it is more acceptable to the patient since they need only have some jelly put on their skin, only make one visit to the X-ray department and they don't have to take unpleasant tablets and perhaps have the pain of the disease increased by taking a fatty meal. However a study by De Lacey *et al* (3) showed that while oral cholecystography had a false negative rate for stones (*i.e.* missing them) of 2·8 per cent, ultrasound had a false negative rate for stones of 4·2 per cent. The false negative rate for missing disease and calling the gall bladder normal when it was in fact diseased was 3 per cent for oral choleycstography but 13·8 per cent for ultrasound. This is because not all gall bladder disease is caused by stones or associated with stones. Acalculous cholecystitis is a very significant clinical problem. There is also the problem of wishing to be able to tell a patient unequivocally that their gall bladder is normal and for this an oral cholecystogram is undoubtedly better. If the gall bladder takes up the contrast medium, concentrates it densely and contracts after fat it can be shown to be physiologically normal and operating in the way that gall bladders normally do. The sign of a diseased gall bladder on oral cholecystography is that the gall bladder does not become opaque. This cardinal cholecystographic sign has been claimed by the enthusiasts for ultrasound to mean that no information is produced but it is quite rare for a gall

bladder that fails to become opaque on oral cholecystography to be shown to be normal.

The cost of oral cholecystography and an ultrasound examination of the gall bladder, excluding capital cost, rent, rates and material, depends upon the time spent by the staff in dealing with the patient. So far as I know no accurate measurements have been made of this time and so costings have to be based on assumptions. Making certain assumptions on this timing, I can make the cost for oral cholecystography come out at £6.91, while the costs of ultrasound of the gall bladder come out at £9.59. Other people, I have no doubt, can make the costs come out at a quite different level and this will be certainly so if one adds in the cost to the patient of having to travel to the hospital on two occasions instead of one occasion.

It has been suggested that since the two examinations are complementary, both should be done. This of course will increase the cost, perhaps doubling it and it is doubtful if by doing both tests in all patients one does in fact increase diagnostic accuracy. I would suggest a more selective method, that is to use oral cholecystography as the first investigation since it is the better test and use ultrasound to assess difficult cases.

This case study was not chosen because it gives a clear answer but rather because it illustrates that clinical practice, costs and benefits depend upon the assumptions that are made. We must be aware of the point raised by De Lacey that 'the possession of, or enthusiasm for, new equipment or a new skill does not mean that it is an improvement on the old'. Ultrasound is very operator dependent. It depends upon the operator knowing the machine. It depends upon the operator knowing how to do the examination. It depends upon the operator understanding the disease he is investigating.

Conclusion

Ultrasound is an important imaging technique comparable to X-ray imaging but having different fields of application, it is truly complementary. It is cheaper than some recent innovations in imaging techniques and is more acceptable to the patient as well as being more versatile. In the decade ahead its

position will be consolidated by technical improvements in apparatus and better understanding by physicians of its use in particular circumstances.

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DISCUSSION

The question was raised as to what extent ultrasound screening should now replace conventional X-ray examination. Ultrasound is indicated in pregnancy as it has no harmful effects on the foetus. In one Department ultrasound had now replaced cholecystograms and it was noted that a lot of costly angiography can be avoided by using ultrasound. Ultrasound is not so satisfactory for screening the skeletal system as X-rays. Replacing X-ray equipment and screening rooms costs much more than updating ultrasound equipment.

Professor Worthington was strongly of the opinion that before we reach final decisions on the relative merits of the screening techniques available, or abandon any of them, more research should be carried out on the relative merits of these different methods. More investment in evaluation is needed. We must put money into all of them but to a different degree determined by their effectiveness for different purposes. First it is necessary to establish the criteria for making priority judgements.

5

STEREOTACTIC RADIOSURGERY

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Stereotaxy is the name given to the art of approaching indirectly, through small holes in the skull, structures within the intracranial space. Stereotactic radiosurgery uses the technique of stereotactic localisation to direct precisely external beams of ionising radiation.

There are a number of intracranial conditions whose operative treatment is still associated with a considerable morbidity or mortality despite advances, which include the use of the operating microscope and advances in anaesthetic and surgical techniques. This may be because of the lesion's depth and inaccessibility as with tumours of the pineal region, or because of their close relationship to arteries, as with arteriovenous malformations, or to nerves or other vital structures, as with acoustic neuromas. Such is the risk, even in the best hands, of brain damage or nerve palsies that some patients are managed conservatively despite the progressive nature of the disease and increasing discomfort and handicap. Even in sites where access is not too difficult, like the pituitary region, direct surgery still involves risks such as haemorrhage, infection or cerebrospinal leakage.

Since the beginning of this century external radiation has been used, with varying degrees of success, to slow or arrest tumour growth and in attempts to provoke thrombosis in vascular malformations. The efficacy of conventional radiotherapy in arresting tumour growth is determined by the effects of radiation on the target tissue but the size of the dose is limited by the radiosensitivity and the functional importance of the adjacent normal tissues. This limitation can be minimised by using accurately directed narrow beams of

gamma irradiation from multiple sources with precise placement of the central zone of cross-firing over the desired target. Such a system, using gamma rays from multiple cobalt 60 sources was designed by Professor Lars Leksell (1) in Sweden and was in clinical use in the Sophiahemmet Hospital in Stockholm in 1968. A second prototype, capable of more variable dosimetry, was installed at the Karolinska Hospital in 1973. A third generation gamma unit of Leksell design, manufactured in Geneva, was installed in Sheffield in late 1984 and became operational for the treatment of patients in September 1985. The project is funded directly by a five-year research and development grant from the DHSS.

In the Sheffield unit 201 small cobalt sources are placed spherically in an outer helmet housed in a large protective dome. The gamma rays from these cobalt sources are directed through narrow tubes or collimators towards a central point. An inner helmet with similar narrow tubes is attached to a hydraulically operated bed. When activated the shutter shielding the gamma ray sources opens and the bed moves hydraulically inwards until the inner and outer collimators meet and cross radiation of the central target point takes place.

The inner collimators can be changed to vary the size of the radiated volume, 4, 8, 14 and 18 mm sizes being available. The apparatus was manufactured in Geneva, with cobalt from California, inserted in the Swiss Atomic Energy Centre and then transported to Sheffield by boat and train.

Preliminary testing showed that the distribution of radiation obtained within the apparatus correlated closely with that calculated in advance on theoretical grounds. The accuracy of the stereotactic method was also confirmed *in vitro* before the patients were exposed.

Treatment is carried out by identifying the size, shape and position of the patient's lesion, by angiography or computer tomography with a coordinate reference frame attached to the patient's head by four pins drilled into the outer table of the skull. The coordinates obtained enable the target to be precisely localised in relation to the base ring. The appropriate size of collimators is then chosen so that the 50 per cent isodose curve correlates to the intended target volume. With larger or irregularly shaped lesions more than one target point

can be chosen. A computer programme enables the total isodose distribution of the combined overlapping fields to be calculated exactly.

After the equipment had been fully tested it became operational when the first patient was treated in September 1985. Since then the plan has been to treat two patients a week, with some allowances for servicing and holidays.

This is almost an outpatient procedure and the patient, after two days on the ward for assessment, is allowed home the day after treatment. Ninety per cent of cases are performed under local anaesthetic, but children under 12 and a small number of adults, for special reasons, have their treatment under general anaesthetic.

Since the Sheffield gamma unit has been in operation, over 130 patients have been treated; 100 with arteriovenous malformations, 15 with acoustic neuromas, 15 with hypersecreting pituitary adenomas and a small number of assorted tumours ranging from meningiomas and haemangioendotheliomas to brain-stem gliomas. To obtain results from a larger series followed over a significant period of time one has to turn to the experience in Stockholm where the Leksell system has been in use since 1968. By 1980 462 patients had been treated by radiosurgery in Stockholm (*figure 5.1*). All the data shown in *figures 5.1–5.3* are from Stockholm (personal communication).

In this account it is only possible to discuss in detail three main areas of proven clinical usefulness. The first of these is in patients with cerebral arteriovenous malformation unsuitable for surgical excision. Very rarely such malformations may thrombose spontaneously and it has been known for half a century that this possibility is increased if the abnormal vessels are irradiated. Nevertheless with conventional radiotherapy the success rate was found to be so low that most centres throughout the world had abandoned the method. In Stockholm Steiner (*figure 5.2*) was able to achieve an excellent success rate in those patients whose arteriovenous malformation was small enough to be included within the 50 per cent isodose curve, using a central dose of 5,000 cGy. He showed that there was a long latent period with no cases obliterated by 6 months, nearly 40 per cent at one year and over 80 per cent

Total number of patients 462	
250 on Prototype I at Sophia Hemmet	
212 on Prototype II at Karolinska Hospital	
Approximately 40-60 patients a year	
392 patients from Sweden	
70 patients from other countries (45 of these with arteriovenous malformations)	
Diseases treated	
Arteriovenous malformations	90
Pituitary tumours	60
Craniopharyngioma	25
Nelson and Cushing's syndrome	20
Hypophysectomy for metastasis	8
Acoustic neuroma	40
Trigeminal neuralgia	60
Arterial aneurysms	5
Gliomas	50
Meningioma	5
Lindau tumours	2
Glomus tumours	1
Pain	72
Ruminative and compulsive neurosis	22
Parkinsonism	2
(Animal experiments	65)

FIG. 5.1. Patients treated by stereotactic radiosurgery in Stockholm as at January 1980

Number of cases	*Latency*	*Total obliteration*	*Partial obliteration*	*No changes*
81	1 year	32 (39·5%)	33 (40·7%)	16 (19·7%)
63	2 years	53 (84·1%)	7 (11·1%)	3 (4·7%)

FIG. 5.2. Stereotactic radiosurgery in arteriovenous malformations, Stockholm 1982. Results one and two years after irradiation.

at 2 years after radiosurgery as confirmed by angiography. Our own experience in Sheffield, although we have only reached one-year follow-up is almost identical even though we have undertaken treatment of larger malformations with up to seven overlapping fields. This rate of thrombo-obliteration has been achieved with virtually no side effects although one patient had a non-fatal rebleed before the malformation had been obliterated and another had an ischaemic complication following the follow-up angiogram after one year. Untreated these malformations are dangerous and give rise to symptoms of intracranial bleeding, epilepsy or progressive neurological deficit. Fifteen to 20 per cent of patients can be expected to have died from intra-cerebral or subarachnoid haemorrhage during an observation period of 12–15 years. The long latent period of many months makes radiosurgery unsuitable for the treatment of bleeding arterial intra-cranial aneurysms where the risk of rebleeding is much higher than in arteriovenous malformations. However there may be a place for it in the prophylactic management of aneurysms which have not bled, found by chance or in patients with multiple aneurysms.

The second area of interest is in the management of patients with acoustic neuroma. Anatomically these tumours are intimately related to facial and trigeminal nerves as well as the acoustic and vestibular components of the eighth nerve and the brainstem. Many patients are elderly and surgery is difficult and dangerous. Furthermore patients with multiple neurofibromatoma, Von Recklinghusen's Disease, often have bilateral acoustic neuromas which makes the preservation of hearing and postponement of surgery, as long as possible, at least on one side, very desirable. *Figure 5.3* shows the degree of preservation of hearing in nine of the early cases in the Stockholm series who still had some hearing at the time of presentation. In 1983 in a series of 120 patients Noren (2) was able to claim containment of tumour growth in 90 per cent of the predominantly small, acoustic neuromas treated radiosurgically. Nearly 10 per cent of patients suffered facial or trigeminal nerve deficits a few months after radiation but these were invariably both incomplete and transient. Unfortunately, the morbidity may prove higher and the success rate lower in large tumours.

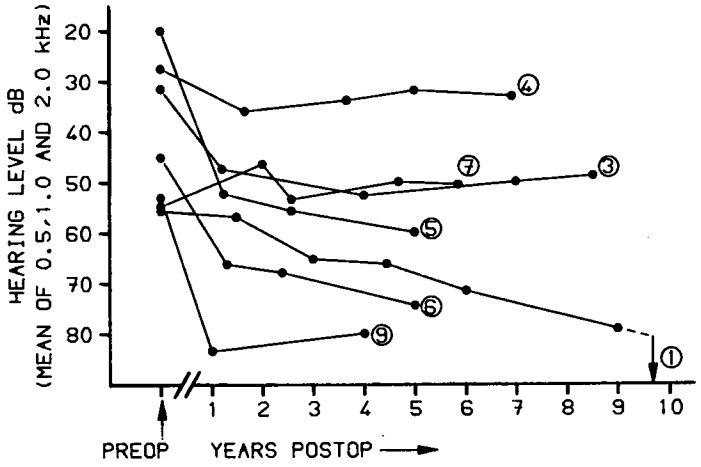

FIG. 5.3. Preoperative tone threshold values and postoperative course of hearing in 7 of the 9 irradiated cases of acoustic neuroma (case numbers in circles).

The third area which lends itself to stereotactic radiation is the region within or adjacent to the pituitary fossa. Pituitary adenomas are comparatively common and good as the results are with transsphenoidal microsurgical techniques there is still some morbidity from haemorrhage, cerebrospinal fluid leakage and infection. Surgical excision of solid craniopharyngiomas is also not without risk and in most hands has a depressing rate of tumour recurrence. In Stockholm Dagerblad *et al* (3) have shown encouraging results in the safe control of hyper-secreting pituitary adenomas and Backlund (4) in the management of solid craniopharyngiomas.

The usefulness of stereotactic radiosurgery in the treatment of pinealomas and surgically inaccessible astrocytomas, meningiomas and haemangioendotheliomas has yet to be established in any significant number of patients. The probability is that it will not prove really effective until a means of presensitising the target tissue to radiation, possibly by immunologically directed adjuvant therapy, is developed.

The Leksell gamma unit and the techniques of stereotaxy provide a unique method of irradiating any relatively confined target within the cranial cavity with great precision and a high

dose, single or repeated. The limiting factor in the precision actually achieved in clinical practice is the accuracy of the diagnostic equipment used. Thus if high doses of radiation are to be confined to pituitary microadenomas, intra-canalicular acoustic neuromas or small vascular malformations, access to magnetic resonance imaging, high resolution computer tomography and sophisticated angiographic equipment are essential.

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DISCUSSION

The method which has been described is only suitable for the treatment of the brain. A completely different apparatus would be needed if the method were to be applied to other parts of the body.

Only two or three centres in the world besides Stockholm are using the cobalt beam technique but other centres are using other beams of protons, electrons or neutrons. Implantation techniques are also used for radiating brain tissues.

The advantages of the cobalt apparatus is that it requires very few people to run it once it has been installed. There are few moving parts and it is not necessary to have a lot of scientific back up.

The Sheffield apparatus, which is the only one in the UK, has been made available for patients from all parts of the country.

6

CHILDHOOD LEUKAEMIA

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Although childhood leukaemia has been recognised for just over a century, it is only in the last two decades that therapy has developed to the point where it is possible to say that the majority of patients can be cured. This satisfying achievement has provided a model for the whole field of medical oncology, but has been at the cost of a great deal of time, effort and money.

When seemingly infinite health service demands are being met with undoubtedly finite resources it is timely for health service managers to review the topic and ask whether any foreseeable future developments are likely to match those of the past, particularly in terms of costs versus benefits. In what follows the subject will be considered under several headings; the number of affected children; the clinical features of their leukaemias; present therapy, together with its evolution, organisation and results; the role of marrow transplantation; the effect of the disease on patients' families; and the quality of life for long survivors.

Incidence

Childhood leukaemia is not common. Even if all types are lumped together, the incidence in the Trent Region is only around 4 per 100,000 children per year—a figure which is in accord with other parts of the world where reliable data are available. This means that the average Trent Health District will have two or three cases per year, and General Practitioners with an average sized list may see an affected child only once in 20 years or so.

Classified on the basis of how they are currently treated, four basic types of childhood leukaemia are encountered.

TABLE 6.1. *Types of Childhood Leukaemia: Sheffield Children's Hospital 1973–86*

Type		*Number*	*Proportion %*
ALL	(Acute lymphoblastic leukaemia)	206	83
ANLL	(Acute non-lymphoblastic leukaemia)	36	15
CGL	(Chronic granulocytic leukaemia)		
	Adult type	3	1
	Juvenile type	3	1
Total		248	100

Their relative frequency can be seen from *table 6.1.* Acute lymphoblastic leukaemia (ALL) in one of its forms accounts for the great majority of cases, with acute leukaemias of other types making up most of the remainder. Chronic leukaemia is very rare in children and for the purpose of this review will be ignored.

Most of the children with leukaemia from the North part of the Trent Region are treated at the Sheffield Children's Hospital. They form a demographically defined caseload with no significant distortion due to an excess of any particular type of patient, so can be used to assess the epidemiology of the diseases concerned.

Sex and age

Boys are affected by ALL more often than girls. Of 190 children aged 14 or less diagnosed in Sheffield during the 12 years to 1987, 84 were girls and 106 were boys. This male excess is a general experience, and is most marked among older children. In the age range 8–14 over 60% of the Sheffield

TABLE 6.2. *Age and Sex Discrimination in Childhood ALL*

Years	*<1*	*2–7*	*8–14*	*Total*
Boy	11	57	38	106
Girl	11	50	23	84
Total	22	107	61	190
Proportion Boys (%)	50	53	62	56

patients were boys (*table 6.2*). Age itself is not normally distributed. There is a hump between the years of two and six with a distinct peak at three (*figure 6.1*).

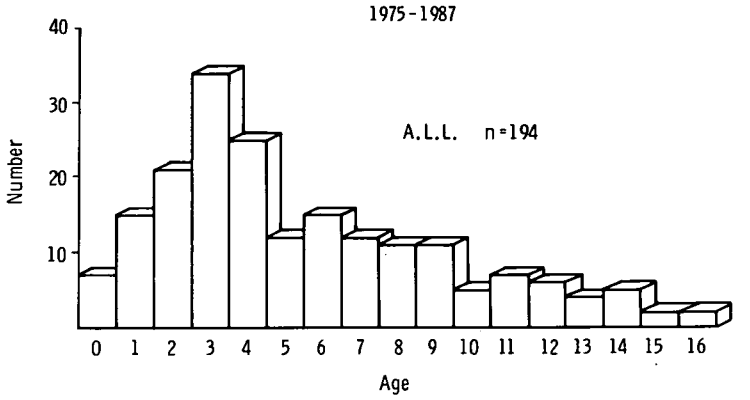


FIG. 6.1. Age distribution in 194 consecutive children with ALL seen at the Sheffield Children's Hospital.

These features of ALL are in sharp contrast to the acute non-lymphoblastic leukaemias (ANLL). Although there are far fewer of them, such diseases arise at all ages with equal frequency (*figure 6.2*) and are evenly distributed between the sexes.

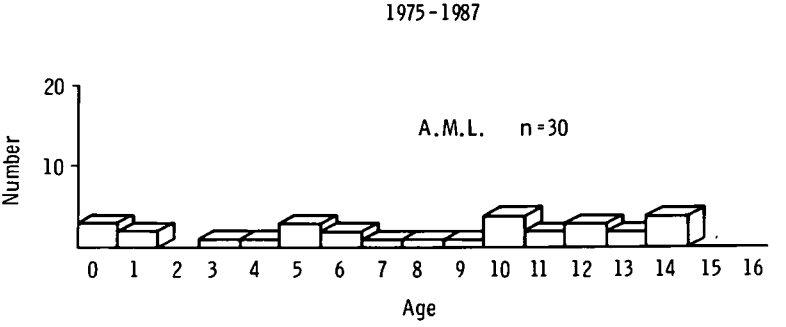


FIG. 6.2. Age distribution in 30 consecutive children with Acute Non-lymphoblastic Leukaemia (ANLL) seen at the Sheffield Children's Hospital.

Diagnostic and Prognostic Features

All leukaemias have one thing in common—malignant cells circulate in the blood and infiltrate the bone marrow. Death is usually caused by bone marrow failure and its resulting agranulocytosis (lack of normal white cells) and thrombocytopenia (lack of platelets).

The commonest way for ALL to present is with some manifestation of bone marrow malfunction—anaemia, infection or abnormal bruising. This can be spectacular, but is more usually insidious with lassitude and pallor. The diagnosis is often not considered at first, and a common story is one of several visits to the doctor over some weeks. About one child in five may present with other signs and symptoms—enlarged lymph nodes, vague bone pains or, more rarely, headaches due to central nervous system infiltration. Conditions with which ALL can be confused include aplastic anaemia, immune thrombocytopenia, juvenile rheumatoid arthritis, bone tumours, brain tumours, meningitis, and even so-called 'irritable hip'.

ALL is not a single disease but a mixture of different diseases—an assumption which is supported by the variability of clinical features, cytomorphology (what the cells look like), cytogenetics (their chromosome content), membrane immunology (their surface structure), cytochemistry (their chemical contents) and arrangements within their genes. How many distinct varieties there are is hard to say, but it is useful to recognise at least four which behave in clinically distinct ways (*table 6.3*). These four are identified by a variety of techniques and differ in their age and sex distribution, their pattern of organ involvement and malfunction, and in their response to treatment. Null ALL and B ALL convey a worse prognosis than T ALL and C ALL.

Also important are some empirically recognised clinical and morphological features which carry a poorer prognosis in terms of survival and which are not specifically confined to one or other of the four ALL types referred to above. The most important of these are as follows:

Diagnostic white cell count high

Male sex

Age less than one year or more than seven

TABLE 6.3. *Clinically Distinct Varieties of ALL*

Type	*Recognised By*	*Special Features*	*Proportion* of total %*
'Common' ALL	A specific cell marker	Multiple extra chromosomes	72
Thymic ALL	T lymphocyte features	Mediastinal mass	12
B ALL	B lymphocyte features	Bulky abdominal disease	1
'Null' ALL	None of the above	L2 morphology	15

* Based on a 5 year cohort of Sheffield children with ALL (n = 69), 1982–87.

Why they relate to prognosis is not clear. Sex and white count at diagnosis both have a marked relationship to survival. It is interesting to note that they have different influences on treatment outcome in terms of time. The white count effect disappears after two years at which time high count survivors have as good a chance subsequently as anybody else, whereas the sex difference does not emerge until the white count effect has disappeared (1). In other words a high white count confers a risk of early treatment failure whereas sex exerts its effect in terms of late, off treatment, relapse.

Treatment itself and the speed of response to it are important prognostic factors, and can override others—which is why the significance of some prognostic features varies from time to time and report to report. Also often ignored, two 'pseudoprognostic' factors need to be taken into account. These are exclusion criteria for any given study and its method of analysis. It is quite possible to generate a 20 per cent improvement in long term results if certain groups (the under one-year olds and B ALLs, for example) are excluded from a trial, particularly if the results of treatment are expressed as 'duration of remission' instead of 'disease free survival'. The former method takes no account of early deaths or deaths in remission which are treatment failures and should be recognised as such.

Current Therapy

ALL and ANLL (acute non-lymphoblastic leukaemia) are treated differently. Over the years more experience has been gained and progress made with the former, though some

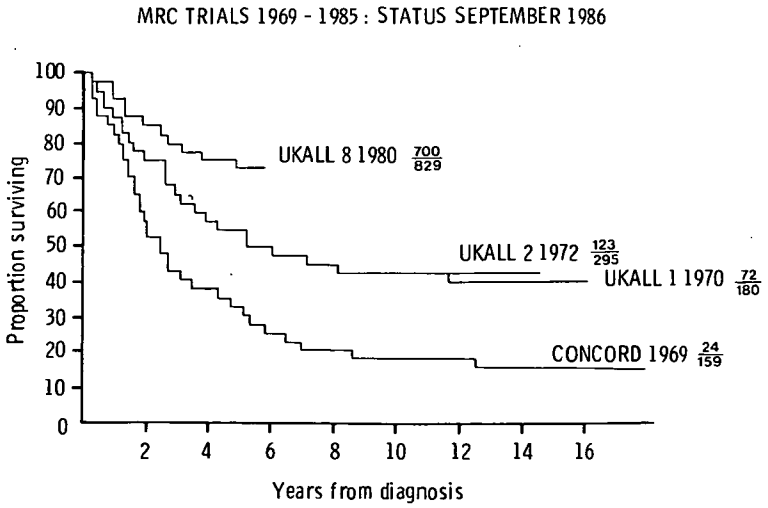
improvements have recently been made with the latter. This review will concentrate on ALL.

Prior to the development of cytotoxic drugs in the late forties, only palliative treatment was available and the median survival from diagnosis was three months (2). Although Farber and his colleagues showed as early as 1948 that the disease could be made to remit (3), it was over 20 years before the word 'cure' was being used with any confidence (4).

The basic triphasic design of current treatment regimens (remission induction, consolidation, continuation) was forged during the 1970s in the UK and elsewhere as a result of a series of multicentre trials. These trials not only helped to shape therapy but also established a pattern of centralisation of patient care where resources and experience could be concentrated; a pattern which is now highly developed (see below).

There have been three main historical eras of therapy which are depicted in *figure 6.3.* Prior to the Concord study in 1970 (5), multi-agent chemotherapy had not been used in a national trial in the UK, and the results were not really impressive until the introduction of the early UKALL trials in 1971 and 1972 which included prophylactic therapy to the central nervous

FIG. 6.3. Actuarial survival of children in successive Medical Research Council Leukaemia Trials.



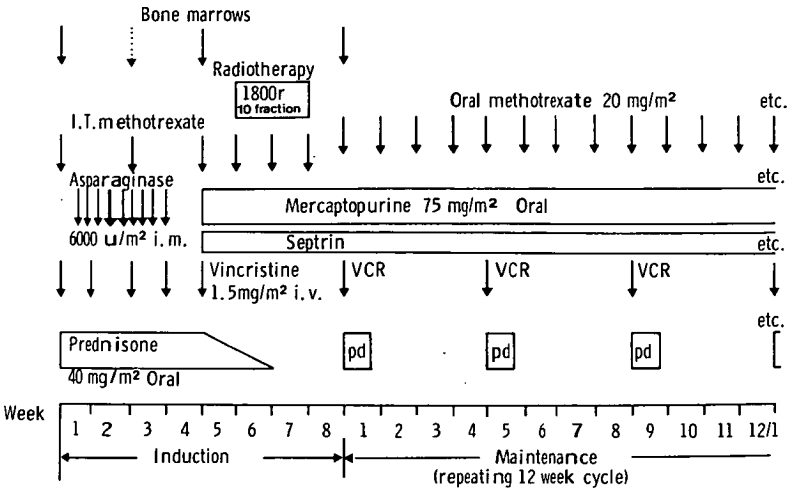


FIG. 6.4. UKALL VIII basic protocol.
IT MTX = Intrathecal methotrexate
VCR = Vincristine pd = prednisone
Total treatment time 2 versus 3 years (random)

system (CNS) and extended treatment time to two years. A lot of experience was gained during the series of UKALL trials from I to VII (6), but disappointingly little improvement in results occurred as they evolved. This fact was made more worrying by the discrepancy in long term survival rates that became apparent towards the end of the seventies between American and British children despite UK treatment protocols being apparently the same as those in the USA.

To find out the reason for the transatlantic difference, in 1980 a US Children's Cancer Study Group protocol was adopted verbatim for use in the UK. This formed the basis of UKALL VIII which began in 1981 (*figure 6.4*). The regimen did not appear to be different in any important respect from earlier UKALL protocols, having the same basic design, but now, seven years later, it has produced a 20 per cent improvement in long-term survival (6) which can be seen in *figure 6.3*.

The reasons for this improvement are not clear, but it seems probable that the previous American:British difference was due at least in part to UK clinicians exercising greater clinical freedom in protocol interpretation and inadvertently under-treating their patients in an attempt to avoid drug-induced marrow failure and its associated morbidity.

While UKALL VIII was in progress, apparently even better results were being reported by the Berlin Frankfurt Munich (BFM) co-operative group in a series of small non-randomised studies which attracted widespread attention (7). The German approach was to give one to two month 'blocks' of intensive combination therapy either early or late in the course of treatment, superimposing these on the standard and internationally agreed triphasic template referred to above. So far the BFM results have not been bettered, but if analysed carefully are probably not significantly different from those of UKALL VIII.

In summary, it can be said that today some three-quarters of children with 'standard risk' ALL will become long-term survivors and have every prospect of cure. The current UK

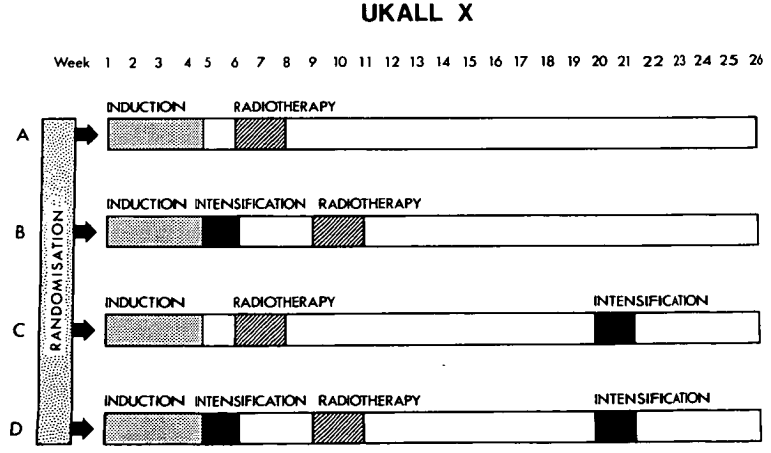


FIG. 6.5. UKALL X trial design
Four-way randomisation exploring the role of the early intensification, late intensification, both or neither
('Neither' = UKALL VIII, see *figure 6.4*).

MRC study is exploring the role of German-style intensive 'block' therapy, now in the context of a prospectively randomised controlled trial (*figure 6.5*). The trial has been open for only two years, so no conclusions can yet be drawn from it.

Organisation of therapy

Nowadays it is unthinkable to leave a child with ALL untreated, but 25 years ago there was a strong body of opinion that to do otherwise was meddlesome, of questionable ethics, and merely protracted a painful inevitable death. This remarkable change has been in large part due to the systematic collection of information by investigative therapists in collaborative studies that have been organised in the UK by the Leukaemia Steering Committee of the Medical Research Council.

The first MRC trial was conducted in the mid-sixties, involved only a few enthusiasts, and recruited less than 150 patients. In contrast, UKALL VIII amassed over 800 children from 17 Regional centres all over Great Britain, and now the rate of recruitment to the current trial, UKALL X, is nearly equal to the total annual number of patients with ALL arising in the UK—approaching 400 per year.

In the early days the only reason general paediatricians did not refer their patients to special treatment centres was to allow them to die in peace, but a different tendency temporarily appeared in the 1970s. When treatment began to look easy and was proving effective, at least in the medium term, there was a great temptation for many physicians in District hospitals to retain their patients and treat them locally to avoid the inconvenience of their having to travel to a tertiary referral centre. This was understandable, as there was no hard evidence to suggest that results of treatment locally under such circumstances were inferior; but there was a drawback. Information on 'peripheral' patients was lost in many instances, and they indirectly slowed down the speed with which therapeutic questions could be answered in MRC trials due to the inextricable link between numbers and statistical power. 'Peripherals' were treated on a variety of

regimens including MRC protocols—without the information feedback—or on other schedules, chiefly American, drawn from published reports.

There has now been a complete reversion to centralised care in most parts of the country. Even where occasional patients are still treated in the Districts, it is now usual for this to be carried out with the help and supervision of Regional centres through which the children concerned are *bona fide* trial entrants. The change has resulted from the evolution of more intensive therapy and the consequent sharp increase in treatment related morbidity, particularly during the first two months after diagnosis where the problems encountered call for specialised nursing care at high dependency levels. The nursing skills required can only be generated and maintained by a sufficiently large caseload to provide the appropriate breadth of experience, and the necessary resources can only be justified in a small number of units where they are going to be used effectively and efficiently.

To persuade any remaining sceptics, convincing data have now been collected which indicate that there is a definite advantage in centralised care for children with ALL. The Childhood Cancer Research Group (CCRG) recently examined survival rates for over 3,000 UK children diagnosed during the seventies based on whether they were in an MRC trial or not and on the caseload size of the unit in which they were treated. The data were collected through the co-operation of the National Cancer Registration Scheme and the Medical Research Council Working Party on Leukaemia in Childhood.

From *figures 6.6 and 6.7* it can be seen that there was a substantially better survival rate for children in the trials and for those treated in centres receiving more than six new patients each year. The reason for these differences does not appear to be that the non-trial, small centre patients contained an excess of children with a particularly poor outlook since such patients appeared to be evenly distributed. The CCRG themselves concluded that therapy according to controlled clinical trials at centres treating large numbers of children has 'had a major impact on the mortality from childhood ALL' (8).

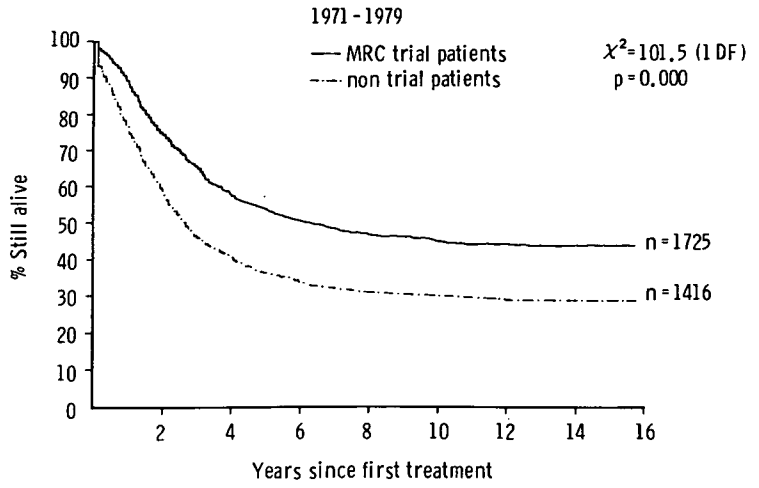


FIG. 6.6. Actuarial survival for 3141 unselected UK children 1971–1979 based on whether they were included in MRC trials or not. (By courtesy of Charles Stiller and the Childhood Cancer Research Group (8)).

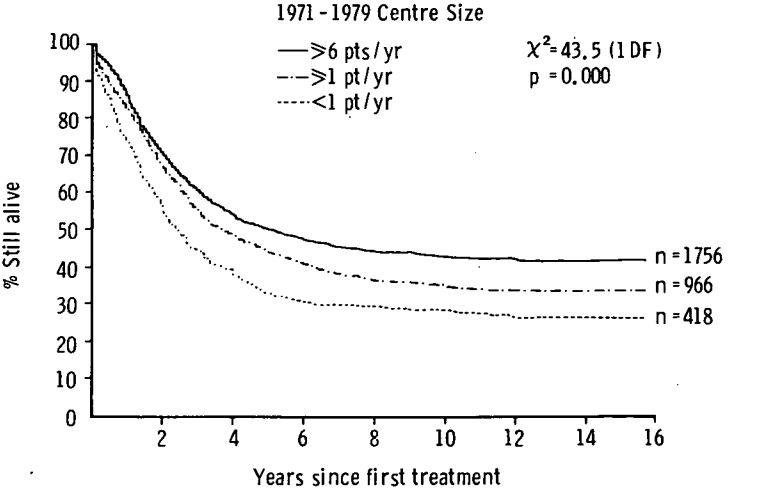


FIG. 6.7. Actuarial survival for 3141 unselected UK children 1971–1979 based on the size of caseload in the centre where they were treated. (By courtesy of Charles Stiller and the Childhood Cancer Research Group (8)).

Bone Marrow Transplants for Childhood Leukaemia

In conditions such as thalassaemia and the various inborn errors of metabolism, marrow transplantation is a way of replacing a defective cell line in the recipient—in other words the transplant itself is the therapy. This is not primarily the case for leukaemias. Here the transplant is a rescue procedure to salvage the patient from otherwise lethal radio- and chemotherapy. Such therapy is normally limited by marrow toxicity, and if overdone will lead to death due to irreversible marrow failure. Avoiding that effect by replacing the burnt-out marrow allows the therapist to explore a greatly increased dose range of drugs and to employ total body irradiation. The limit of such treatment is then mortal toxicity to the next most sensitive organs, the gut or the heart, but these organs are much more resilient than marrow.

A fundamental difference between transplanting marrow and any other organ is that marrow is transfused as stem (seed) cells which have the capacity to grow in the recipient whereas other organs are physically grafted into the recipient as preformed structures. Technically, marrow transplants are very simple and require no surgery. Marrow-containing blood is aspirated by many needle punctures from the donor's pelvis and is then given to the recipient intravenously through an ordinary blood giving set. The marrow cells find their own way to their appropriate environment through the circulation.

The main difficulties involved in marrow transplants relate to immune tolerance. The cells infused in marrow not only generate colonies of red cells and platelets but also produce immunologically competent white cells. These grafted cells recognise the host as 'foreign' and attack various organs, chiefly the skin, gut and liver, causing anything from a chronic rash to a rapidly fatal disease. There is little or no host retaliation, as the host immune system is effectively eradicated by the pre-graft radio- and chemotherapy. Graft versus host disease has been the limiting factor in the rate of application of marrow transplants for many years, and still is. Much effort is needed to control or avoid it, but until further progress is made the use of mismatched or unrelated donors will remain hazardous and experimental.

Using tissue matched sibling donors, on the other hand, marrow transplants are now in the realm of orthodox therapy for patients with leukaemia provided certain criteria are fulfilled. Currently these are that the patient should have a five-year survival prospect of less than 40 per cent using conventional therapy, a fully matched healthy sibling donor, should be young (in this context less than 40), and should be in remission from his or her disease at the time of the procedure.

The number of children who fulfil all of these conditions is small. Patients falling into the first category of survival comprise at most only 50 per cent of the total, and given the average family size in the UK, only one in four is likely to have a potential donor. A few patients will have resistant disease and not be fit enough to survive the procedure, which leaves around 12 per cent of all children with leukaemia as possible transplant candidates. For the million children who live in the Trent Region this represents only about five each year.

If the eligibility criteria change and the use of unrelated or mismatched donors becomes easier, this figure could quadruple. It is also likely to increase due to the advent of autotransplantation where the patient's own marrow is harvested, preserved and later returned, possibly having been 'purged' of residual disease in the meantime. Such a procedure is soon to be evaluated in a national trial for acute non-lymphoblastic leukaemia, a trial that will be relevant for the 15 per cent of leukaemia children who have this type of disease. Nonetheless it should be stressed that autotransplantation for leukaemias is still experimental and of unproved benefit.

In the past the prognosis for children with ALL which relapsed during or after a course of conventional therapy was appalling, as can be seen from *figure 6.8*. It is for this type of patient in their second or subsequent remissions, that the bulk of transplants are now performed, together with a few children who have high risk disease in their first remission. So far sixteen such patients have been transplanted at the Sheffield Children's Hospital, and their survival, together with that of two children attending the hospital who had transplants elsewhere, is shown in *figure 6.9*. The 18 transplants are there compared to a matched control group of patients who were otherwise similar but did not have a suitable donor.

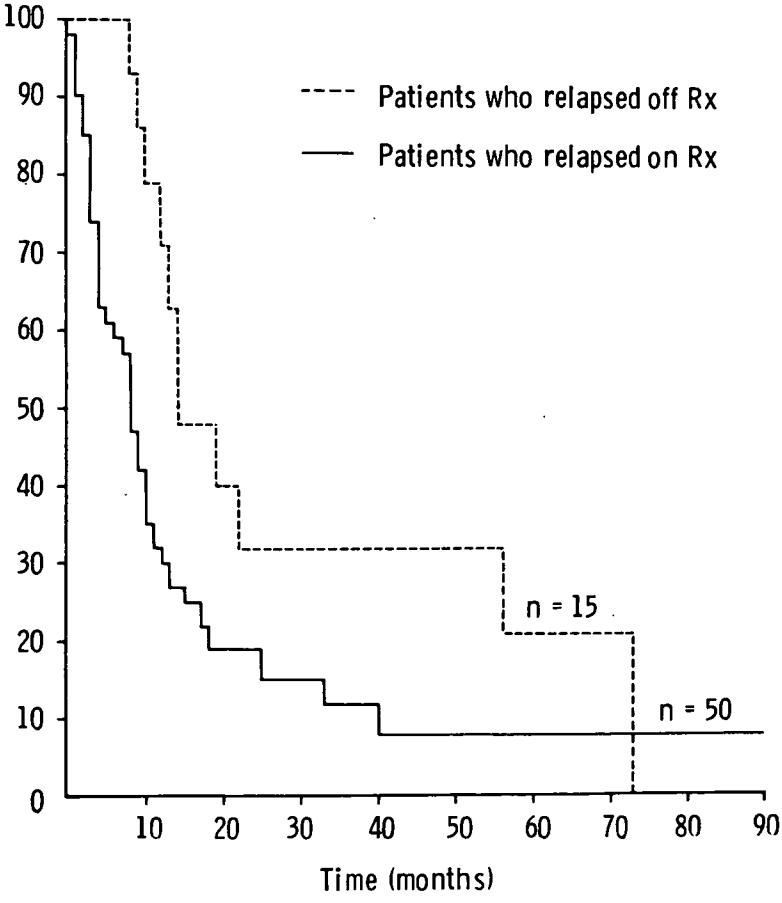


FIG. 6.8. Actuarial survival following relapse in 65 consecutive children treated with conventional therapy at the Sheffield Children's Hospital.

The numbers are small, but the difference is statistically significant at the level of $p<0{\cdot}05$.

Experience from other centres indicates that both of these groups will suffer further losses, and the current long-term survival rate for children with relapsed ALL following allogeneic marrow transplantation is only in the order of 20 to 40 per cent (9). While superficially disappointing, this figure represents the salvage rate from a group with an eventual

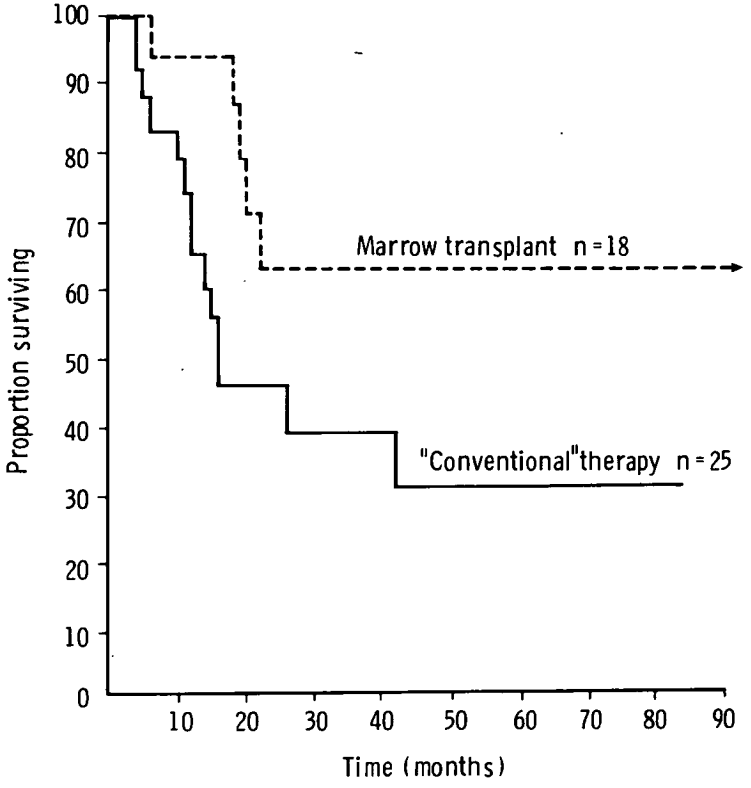


FIG. 6.9. Actuarial survival following marrow transplantation in a group of 18 Sheffield patients with poor prognosis, relapse or *de novo* leukaemia compared with a time- and disease-matched control group. $p < 0{\cdot}05$.

mortality approaching 100 per cent and should be seen in that context. Deaths following transplantation for ALL are divided between complications of post-transplant immune deficiency associated with graft versus host disease, and relapse of the primary leukaemia.

Family Problems when a Child has Leukaemia

The psychosocial consequences for the family of a leukaemic child are variable but always considerable (10). The effect may spread beyond the nuclear family, and last for a very long time.

Perhaps the most easily recognisable and understandable effect of their child's illness on parents is what might be called

the Damocles syndrome. Before effective therapy became available, the diagnosis of ALL prompted immediate anticipatory mourning for an inevitable bereavement. The circumstances were tragic, but everyone knew where they stood. Now it is more difficult. Explaining the likely outcome of treatment in any given patient boils down to saying that the child is probably (or possibly) curable but only time will tell.

It is particularly unfortunate that the risk of disease recurrence does not disappear, but diminishes exponentially with the passage of time. There is no stage at which one can tell parents that their child is cured, and so relieve them of the fear of relapse. The consequence of this is a state of chronic anxiety which waxes and wanes for a variety of reasons many of which are irrational but all of which are quite understandable.

McGuire once said, in the context of breast cancer, that a psychosis is likely to be precipitated by a severe threat, involving loss, which continues for a long time and has a degree of uncertainty about it. That succinctly summarises the leukaemia-associated Damocles syndrome, and makes it easy to understand why marriages break up, alcohol abuse occurs, and sibling behavioural disturbances arise. Yet most families cope. For some the whole experience is regarded as an enriching one—usually in retrospect—which welds the family together. Surprisingly, perhaps, this can be equally true whether the affected child survives or not.

Quality of Life for Long-term Survivors

An obvious concern is that the long-term survivors might have problems due to their disease or its treatment. So far the experience is generally reassuring, and for the majority of patients sequelae seem to be minimal. Males are generally subfertile (sterile if they have had testicular radiotherapy as some have for leukaemic infiltration), but female fertility seems unimpaired. Growth is slowed down for the period on therapy, but generally catches up afterwards, and secondary growth failure is rare. A few children who have had their spine irradiated develop a disproportionately short trunk. Most children progress through puberty uneventfully, though occa-

sional boys, again the recipients of testicular radiotherapy, need hormone supplements.

Cranial radiotherapy doses have been generally reduced in more recent years due to modest intellectual impairment being detected in recipients of the earlier higher doses. It is now recommended that no child is irradiated until the age of two as young infants are particularly prone to such damage.

A few second malignancies have been seen, both leukaemias and solid tumours. In most instances these seem to be treatment induced and are similar to those seen in long survivors of other malignancies such as Hodgkin's disease. Very occasionally what appears to be the original disease can relapse late—up to seven years after diagnosis (11), but this is a very infrequent event. It might be expected that transplant survivors would be particularly prone to later malignancy due to the total body irradiation and (frequent) high doses of cyclophosphamide—a notably carcinogenic drug. So far if this is so it has not become widely apparent. Leukaemia in the donor marrow has been described (12), but the anticipated excess of true secondary leukaemias has not yet materialised.

Summary and Conclusions

Around 400 children in the UK will develop acute lymphoblastic leukaemia each year, of whom between two-thirds and three-quarters will be permanently cured given the best available therapy. Such therapy now demands high dependency care from specially trained medical and nursing staff, but if successful is cost effective as the quality of life in the survivors is usually normal apart from male subfertility.

The cost of failure is high, both in human and financial terms. For the future, conventional therapy needs further refinement to increase its success rate, and marrow transplantation needs further development as a back-up should primary treatment fail. If these objectives can be achieved, childhood ALL could soon be reclassified as a readily curable disease in all but a few cases. For the few children who have other types of leukaemia, the outlook is not so good. For them controlled experimental therapy is required in a few centres to provide information on how best to improve their prognosis.

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DISCUSSION

It was suggested that methods of molecular biology might contribute to more precise prognosis in cases of leukaemia during the next ten years.

Dr Lilleyman had largely confined his remarks to acute lymphoblastic leukaemia (ALL) in childhood. If adults are

included in the discussion it should be noted that acute myeloid leukaemia constitutes the biggest problem numerically. Autologous transplants which are on trial for this condition in adults might also be tried for children with myeloid leukaemia.

Considerable discussion took place on the desirability of referring cases of ALL in childhood to special centres. This now occurred to a large extent in the UK and this has been followed by a greatly improved prognosis for ALL. It required the disciplined co-operation of paediatricians and in financial terms involved the allocation of extra funds for these special centres. There was a need to establish the costs and benefits of the treatment of ALL. It was agreed that this was a most difficult task both to measure the costs and to assess the benefits. There were other special forms of treatment such as liver transplantation where centres should be national or supra-Regional and these again posed difficult problems in the allocation of resources as well as social problems resulting from the patient being removed far away from his or her home. The difficulties of keeping up-to-date experienced by some consultants working a long way from their teaching hospital centre was mentioned as a further argument for referring patients requiring highly technical types of treatment to special centres.

The question of radiation-induced bone cancers in patients treated with irradiation was briefly discussed and Dr Lilleyman said he had had personal experience of four such cases in Sheffield since 1978.

One speaker asked whether the incidence of leukaemia was changing and whether the Chernobyl disaster was likely to affect the incidence. Dr Lilleyman thought that Chernobyl would probably not have a statistically or clinically important effect in the UK.

7

OSSEOINTEGRATED DENTAL IMPLANTS

PROFESSOR R B JOHNS

Professor of Restorative Dentistry, University of Sheffield

There is nothing new in the problems posed by the loss of teeth. To some patients the loss of all teeth is no more than a minor inconvenience, to others it heralds in a phase of life which is miserable and is regarded by them as a severe loss in the quality of their life. The reasons for patients becoming edentulous are many—some arrive in this condition as a result of fear of the dentist and fail to seek advice until remedial treatment is no longer possible. Neglect of even the most basic care of teeth has in the past accounted for many finding themselves in an edentulous state while still young adults.

It is ironic that the dental profession itself is not altogether blameless in accounting for patients losing their teeth unnecessarily. Over-enthusiastic restorative treatment, a desire to replace rather than to repair even the slightest defect in a restoration, has been shown to lead to the loss of tooth substance to a point where no more restorative treatment is possible (1). In this country a service has been provided since 1948 which has positively encouraged this approach. Unfortunately, 'market forces' do appear to influence the pattern of treatment provided by dentists.

Furthermore, in relatively recent times there was an attitude in some social groups which encouraged wholesale extraction of teeth and the provision of complete dentures as a way of ensuring trouble-free eating and as a long term economy. The ravages of this approach are still apparent and undoubtedly contribute to the national statistic that 25 per cent of the population over the age of 20 are edentulous (2).

The response of dentists to the problems presented by the

edentulous patient, who finds conventional complete dentures functionally, aesthetically and socially inadequate, has often been less than sympathetic. It is conceded within the dental profession that in terms of function the efficiency of dentures is rarely greater than 10 per cent of their natural counterpart. Aesthetically, the achievement has depended to a very large extent on the cost of materials used and the time and expertise of the dental technician making the dentures. Again market forces have an important influence on the quality of the end product. The shortcomings of dentures in social terms are acknowledged by dentists but they have little to offer their patients apart from sympathy and what psychological support they are capable of giving.

Coerced by apocryphal stories, patients have beseeched dentists to 'screw teeth into the gums' for many years. Success, however, has for the most part been short-lived and where high success rates have been claimed these have never stood up to peer scrutiny. The reasons for the occasional success of a few implants could no more be explained than the failure of the many. The designs and materials which have been employed over the last 180 years are many but none, until the work of Branemark and his team (3), has gained acceptance by virtue of the normal criteria of scientific investigation.

The fundamental research which was conducted in Gothenberg by the Branemark group of workers was attempting to answer the question of bone reaction to thermal trauma (4). The significant result of these studies demonstrated that if the temperature of bone were raised and sustained for more than one minute at 47° C there would be bone necrosis and delayed healing.

The test cell which was constructed for this work was made from commercially pure titanium, a metal recognised as being almost completely inert in the tissue environment. When the device was removed at the conclusion of the experiment it was found that it had integrated with the bone through which it passed. It was as a result of this observation that Branemark and his team realised that there were a number of orthopaedic problems which might be solved as a consequence of this phenomenon. Edentulism was seen as just one such problem.

The technique developed by the Gothenberg team depends

on two fundamental principles. First, the preparation of the bone to receive the implant must cause the absolute minimum of trauma. Secondly, the oxide layer which surrounds the titanium must not be contaminated by any other metal or protein (5).

Another remarkable aspect of the work of the Gothenberg team lies not only in the meticulous engineering of the implants and care of the tissue but in their evaluation of the system they devised. Very little of the technique was published until nearly 4,000 fixtures (implants) had been inserted and followed for periods of up to ten years. This policy has put the Gothenberg team and the company (Nobelpharma) which has supported them and helped in the development, in an immensely strong position. Any competitor who feels their product is an improvement on that developed by Nobelpharma must be prepared to have their results compared to what is now a 20-year study. The first ten-year study can support a claim of 91 per cent success rate of fixtures in the lower jaw and a prosthesis retention rate of 100 per cent, while in the upper jaw the comparable rates are 88 per cent and 95 per cent (6).

Patient Selection

Careful selection and education of the patients is of the utmost importance. There must not only be good clinical and radiographic assessment of each patient who is referred to the implant clinic but they themselves must be in no doubt about what is involved and how long it will be before they are fitted with their prosthesis. There must be no equivocation over the disadvantages and difficulties they will experience in the period leading up to the fitting of the prosthesis.

Scope of Treatment Available in Sheffield

Until recently treatment has been confined at the Sheffield clinic to those patients who are edentulous in the lower jaw. All the prostheses which have been used are of the fixed variety, that is, those which are directly attached to the implants and are only removable by the operator. However, prostheses which are removable by the patient and are supported and retained by only two fixtures are now being

fitted. Partial edentulism, including single tooth replacement, is about to be undertaken in the Sheffield centre.

Technique—Surgical

There are two parts of the surgical phase of the technique and these are both carried out under local anaesthesia with sedation. The first operation takes about two-and-a-half hours and the second about one hour. A very high standard in both the operating technique and the operating environment is essential and this stipulation puts this phase of the procedure out of the reach of the general dental practitioner.

At the first operation the lower jaw is exposed from the oral surface. The bone must be visible from the premolar region on one side to the corresponding region on the other. The five or six sites to receive the implants are selected so that they are approximately equidistant from one another and are all anterior to the mental foramina. The direction and depth of each hole which is cut is dependent on the shape, thickness and texture of the bone. The preparation of a hole is undertaken with a series of drills, each of slightly larger diameter than its predecessor in order to minimise the generation of heat. For the same reason there is copious irrigation of the drilling site. The final shaping is carried out at very low speeds (15 rpm) and with instruments themselves made of titanium. The reason for the use of titanium instruments is two-fold. First it is to ensure that any fragments of metal which may be left within the bone from the previously used drill will be removed. Secondly if there are any fragments left behind after the final preparation these will be of titanium and there will be no danger of an electro-chemical cell being established between dissimilar metals which could interfere with the process of osseointegration.

The fixtures themselves are finally rotated into the hole prepared for them, again at a very slow speed. A cover screw is inserted into the top of the fixture and the soft tissue is sutured back into place. A gauze pack is placed over the site of the operation and the patient instructed to bite firmly on this.

Patients stay in a recovery ward for a few hours after the operation before being allowed home. Occasionally patients stay in one night if home care is not available or a long journey

is involved. After-pain has not been a problem for any of the patients treated in Sheffield. It is described as being certainly no more than the pain which follows a normal extraction. It is important that the dentures for the jaw which has been treated should not be worn for at least two weeks after the operation. This is to guard against the risk of an ulcer developing over an implant site with the concomitant risk of infection. Thereafter the previous denture may be modified with a soft lining so that it can serve at least for social occasions if not eating.

After a period of three months, when the lower jaw is being treated, six months for the upper jaw, the second operation takes place. By this time it is believed that osseointegration will have occurred and there will be continuity between the oxide layer surrounding the fixture and the bone. The operation is again carried out under local anaesthesia and sedation and takes about an hour to complete. The tissue is again reflected to expose the upper surface of the jaw and the cover screws inserted in the fixtures are removed. The second component of the implant, the abutment, is then screwed into the implant and the osseointegration tested by tapping the now complete fixture. There is a characteristic metallic ring if integration has been achieved. The tissue is sutured back in place so that the now complete implant penetrates the soft tissue into the mouth to form the foundation for the prosthesis. A healing pack is placed around the abutments and this is removed, together with the sutures, after a week.

Technique—Prosthetic

The prosthetic phase of the treatment depends on an accurate impression being taken of the five or six abutments. Unlike natural teeth, osseointegrated implants are not surrounded by a peridontal membrane and therefore there is no mobility. This demands extreme accuracy when taking the impression. From the impression and the normal records taken for the construction of a denture, a cast gold alloy bar is made and the accuracy of the fit of this is tested on the abutments at the next visit. The cast bar forms the substructure on which the fixed bridge is then made. It should be noted that the bridge may be extended distal to the last abutment by 12–15 mm thus making the two ends of the prosthesis cantilevered.

The bridge, once finally processed, is attached to the abutments by small gold alloy screws which are then sealed within the body of the bridge with a conventional non-metallic filling material. The use of such a material allows the screws to remain undisturbed until the bridge is removed for checking and cleaning approximately a year later. Radiographs are taken of the fixtures once the abutment screws have been fitted and thereafter at the annual inspection.

For the type of bridge fitted in the lower jaw the clearance of 5–6 mm between the underside of the prosthesis and the soft tissue of the jaw is not apparent in normal conversation as the lower lip covers this area. The advantage for the patient in having this wide space is that cleaning, which is most important, is made quite simple.

As soon as such a prosthesis has been fitted patients have been able to bite into an apple immediately and without any discomfort. It is an experience which they have not had since the loss of their natural teeth. The transformation in their attitude to their teeth is remarkable in that they describe the bridge as feeling 'part of me'. In all those who have been treated it is clearly evident that their self-esteem has increased, there is a noticeable relaxation of their circum-oral musculature, which no longer needs to control their conventional prosthesis from becoming dislodged, and an improvement in their 'quality of life'. Indeed this has been a consistent feature remarked on by all those who have been treated using this technique to support their prosthesis.

The treatment of the upper jaw by this method is more difficult as the character of the bone is different from that of the lower jaw. The floor of the nose and the maxillary sinus are at times very close to the oral cavity with little bone separating them. From a prosthetic point of view the tissue lost following extraction needs to be made part of the prosthesis and this more difficult to achieve with a fixed bridge. However, a considerable improvement in retention of an upper denture can be achieved by providing the patient with a removable prosthesis which is held in place by a series of clips within the denture and which themselves gain support from gold bars supported on osseointegrated fixtures. This compromise gives the patient a denture which does not move

when eating or talking, it transmits much of the occlusal load directly to the underlying bone and gives a pleasing appearance by providing support for the soft tissues of the face. Because it is removable by the patient for daily cleaning it thus loses the quality of the feeling of being 'part of me'.

Future Developments

The system of using screws made of titanium to obtain osseointegration must depend on there being adequate thickness of bone into which the screws may be placed. Provided there is a minimum of 7 mm of bone, grafting procedures are now being investigated in the Branemark clinic in Gothenberg.

A procedure which is more advanced in development and is already in clinical use at some centres, is the technique for placing fixtures in those regions of the mouth where only three or four adjacent teeth have been lost. The considerable advantage of this development is that neither conventional bridgework, with the inevitable crown preparations required on adjacent teeth, nor partial dentures, with all their attendant oral and social disadvantages, are necessary. It is now indeed possible, in some circumstances, to replace a single missing tooth with an osseointegrated implant supporting the crown.

Estimates of Cost

Length of time of operative procedures

Based on the experience which has been gained at the School of Clinical Dentistry in Sheffield since March 1985 the time taken in providing surgical and restorative treatment for one patient to have a lower bridge fitted to fixtures inserted in the lower jaw is as follows:

Oral Surgeon	5 hours
Prosthodontist	$6\frac{1}{2}$ hours
Hygienist	1 hour
Technician	15 hours

If this experience were to be extrapolated using the staffing levels in the Branemark Clinic, Gothenberg where approximately 300 patients are treated annually, staff costs based on current NHS salaries would be as shown in *table 7.1.*

TABLE 7.1. *Estimated Staff Costs Based on Current NHS Salaries*

Staff (wte)	*£000*
2 Oral Surgeons	68
2.5 Prosthodontists	85
3 Dental Technicians	60
1 Hygienist	12
6 Dental Surgery Assistants	60
2 Appointment Clerk/Secretary	20
Total staff costs	305
Staff costs per patient treated £1,016	

Materials costs

Again based on the experience gained in Sheffield the cost of all materials, including fixtures, prostheses and depreciation of specialised equipment used for the procedure (assuming that Value Added Tax were charged) would be £2,243 per patient.

For a centre treating 300 patients a year based on staff costs and materials in the UK but excluding all capital costs, the unit cost per patient would be £3,259.

The Cost of Providing Treatment in the Trent Region

At the present time the public and the dental profession are to a large extent unaware of the development which has taken place. Were the 1,087 dentists in the General Dental Service in the Trent Region to refer just one of their patients a year for treatment by this method, the cost based on the above estimates would be £3·5m.

An alternative calculation is to suggest that half of one per cent of all those who are edentulous over the age of 20 (25 per cent) and live in the Trent Region are candidates for treatment by this method. There would therefore be a potential waiting list of 5,750. The cost of treatment for this very small number of edentulous patients would be £18·7m.

There is clearly a need to ensure that this development is not relegated to the status of esoteric treatment for an elite section of society. It is therefore essential that the cost is brought into line with comparable operations which significantly improve the quality of life for a disadvantaged group. To this end there

TABLE 7.2. *Uptake of Treatment*

	Patients treated	*Population (millions)*	*Ratio of Patients treated*
USA	20,000	220	1 : 11,000
Sweden*	10,000	9	1 : 900
UK	200	56	1 : 280,000
Trent Region	30	4.6	1 : 153,000
UK excluding Trent Region	170	51.4	1 : 302,000

* The edentulism in the population over age of 20 in UK is 25%, in Sweden the comparable figure is 6%.

is already a research project, organised by the Gothenberg Clinic, being undertaken in eight centres world-wide, including the centre in Sheffield. The aim of the project is to treat a total of 160 patients, monitor their progress over the next five years and establish criteria for a simplified prosthetic method. It is anticipated that not only will the materials cost be approximately a quarter of present costs but the surgery time will also be significantly reduced. This will allow more patients to be treated at a lower cost per patient.

Demand and need

It is extremely difficult to estimate just how great the need for this form of treatment is in the UK and in this Region. Some form of perspective may be had by reviewing the uptake of treatment in Sweden, USA, UK and the Trent Region (*table* 7.2).

The population of Sweden is approximately twice that of the Trent Region. Were the uptake of treatment in the Region to be the same as in Sweden, the number of patients who would have been treated by the year 2002 (15 years) in Trent would be 5,100.

Conclusion

The technique developed by Branemark in Sweden will have a very considerable effect on the practice of restorative dentistry in this country in the next ten years. Indeed it is likely that specialist centres devoted to this technique will become established throughout the country. At these centres not only

will routine treatment and training courses be provided but they will act as centres of excellence where new techniques will be developed alongside basic research in osseointegration.

The surgical component of the system will need to be maintained by oral surgery departments in general hospitals while the restorative component of the system becomes a regular feature in undergraduate teaching and thus part and parcel of general dental practice.

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DISCUSSION

The high proportion of edentulous people in the North of England was commented on although it was noted that the prevalence has decreased in the last 17 years from about 37 per cent to about 25 per cent. The fall in the number of the edentulous can be attributed to the use of fluoridated toothpaste and the fluoridation of water supplies in some areas and to better dental care. The question was whether more of these edentulous people should be offered dental implants or continue to seek full dentures which often prove unsatisfactory and have to be replaced several times. There was

considerable discussion on the relatively high cost of treatment with implants.

It was pointed out by the Chairman of the Trent Regional Health Authority that it might be difficult when resources were strictly limited to justify this sort of expenditure against claims for expenditure on life-saving treatments. It might be necessary to leave this form of treatment to the private sector.

Professor Johns suggested that implant treatment should be provided in a few selected centres of excellence. He also thought that the knowledge gained might be relevant in orthopaedic surgery in relation to the question of whether to use cemented or non-cemented implants in treating femoral neck fractures. The work on dental implants demonstrated the possibility of achieving osseointegration between implant and bone.

GLOSSARY OF TERMS

Adenoma	A simple tumour of glandular epithelium and connective tissue
Allogeneic	Obtained from another individual of the same species (*i.e.* human)
Angiocardiography	Outlining the heart chambers after the insertion of a tube through the skin and blood vessels and advancing it into the heart followed by an injection of radio-opaque material and the taking of numerous rapid sequence X-rays
Angiogram	A method of outlining a blood vessel after the insertion of a tube through the skin and into the blood vessel by injection radio-opaque material and taking X-rays
Astrocytoma	A tumour of the astrocytic cells of the brain (a form of glioma)
Cholescystography	Examination of the gall bladder by X-ray study
Cholecystitis	Inflammation of the gall bladder
Craniopharyngioma	An intracranial or skull based tumour arising in the remnants of the pituitary duct, usually slow growing
Endoscopy	Looking inside an organ (*e.g.* stomach) by inserting an optical instrument
Glioma	A tumour composed of neuroglio cells and fibres found in the brain or, occasionally, the spinal cord. Usually locally malignant
Haemangioendothelioma	A benign tumour of vessels and connective tissue usually occurring in the posterior part of the brain, often multiple
Laparotomy	An operation involving opening the abdomen
Lymphangiogram	An X-ray outlining the lymphatic vessels by means of radio-opaque material (contrast medium)

Lymphoma A general term comprising tumours, and conditions allied to tumours, arising from some or all of the cells of lymphoid tissue. Sometimes occurring in the brain

Meningioma A usually benign tumour arising from the membranes surrounding the brain

Mental foramina Two small holes on the outside of the lower jaw bone in the premolar region. Damage to the nerves which pass through these holes will result in loss of sensation of the lower lip

Myelography/myelogram An X-ray outlining the spinal cord and nerve roots by injecting a radio-opaque material (contrast medium) into the surrounding pool of fluid (cerebro-spinal fluid) within the spine

Neuroma A tumour composed of nerve cells and nerve fibres

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