Timing of measurements

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<th>Timing of measurements</th>
<th>Intravenous administration</th>
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<tr>
<td></td>
<td>Peak—15 mins after the end of the infusion</td>
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<td>Trough—just before the next dose</td>
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<td>Intramuscular administration</td>
<td>Peak—1 hour after the dose</td>
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Blood samples for serum aminoglycoside measurements are generally taken immediately before a dose (the trough concentration) and soon after the next dose (the peak concentration). Although this is the order in which the samples are taken, it is generally assumed for dosage calculations that the trough concentration is that measured after the peak rather than before it.

The time of sampling for the peak concentration depends on the route of administration. If the aminoglycoside is given by intravenous infusion samples should be taken 15 minutes after the end of the infusion. If the intramuscular route is chosen they should be taken one hour after the injection.


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Monoclonal Antibodies in Medicine

Principles of antibody therapy

Stephen J Russell, Meirion B Llewelyn, Robert E Hawkins

The success of monoclonal antibodies in clinical practice is dependent on good design. Finding a suitable target is the most important part as other properties of the antibody can be altered by genetic engineering. Antibodies that target lymphocyte antigens offer less toxic immunosuppressive treatment than currently available drugs and the first monoclonal antibody approved for human use is an immunosuppressive agent for treating rejection of renal transplants. Human trials of monoclonal antibodies to treat septic shock have been done and antibodies are also being developed to target common pathogens such as herpes simplex virus. Although monoclonal antibodies against cancer have been much heralded, their success has been limited by the poor access to the inside of tumours. Treatment of blood cancers has been more successful and a human antibody against B cell malignancies is being clinically tested. As knowledge about natural immune responses and antibody engineering increases many more monoclonals are likely to feature in clinical practice.

The 1990s will be a testing time for monoclonal antibodies. Potential clinical applications include the treatment of cancer, autoimmune disease, transplant rejection, viral infection, and toxic shock. The Centre for Exploitation of Science and Technology has estimated that the total world market for monoclonal antibodies will reach $1000 million by 1994, rising to $6000 million by the year 2000.1 It remains to be seen whether the clinical promise of monoclonal antibodies will be realised on such a grand scale, but antibody therapy is likely to be much more in evidence in many clinical settings over the next few years. Clinicians will therefore need to familiarise themselves with some of the issues relating to use of clinical antibodies.

As described in the previous article in this series, monoclonal antibodies can be generated against most target antigens, purified, split into fragments, and conjugated to radionuclides, toxins, enzymes, or drugs. The genes can be cloned and reconstructed to give new versions of the antibody with decreased immunogenicity, improved affinity, reduced size, or novel effector domains. For a given clinical application the first task is to choose an appropriate target antigen and then to optimise the therapeutic antibody generated against the chosen target.

Rather than catalogue every antibody with clinical potential or every disease that has responded to monoclonal antibodies, the aim of this review is to underline the principles governing antibody therapy and to illustrate these with specific examples.

Target antigens

Antibodies can neutralise toxins; block the interaction of growth factors, hormones, intercellular adhesion molecules, or viruses with their cognate cellular receptors; and coat bacteria, viruses, or cells, marking them for phagocytosis, antibody dependent cellular cytotoxicity, or complement mediated lysis.

Target antigens can therefore be circulating or on the cell surface. Selecting a suitable target for a given disease depends not only on the aims of treatment but on the precise tissue distribution of the target antigen, its function, and its fate after it has complexed with the therapeutic monoclonal antibody. Finding a suitable target antigen is probably the most important factor determining the ultimate success or failure of antibody therapy. Provided the target has been well chosen it may be possible to modify the corresponding monoclonal antibody in various ways to enhance its therapeutic potential.

Pharmacokinetics

Infused antibodies are diluted almost immediately in the total plasma volume and then diffuse more slowly...
across the walls of small blood vessels into the interstitial fluid (distribution phase). The half life of the circulating antibody is determined by the rate at which it is metabolised and excreted (elimination phase). The degree to which the target antigen is bound varies with the total time of exposure, the concentration, and the kinetic properties of the monoclonal antibody.

REACHING THE TARGET

How easily infused monoclonal antibody can reach it depends on the target’s location. Intravascular targets are readily accessible, but other targets are less easily reached because exit from the vascular system is restricted. To gain access to extravascular targets (for example, cancer cell surface antigens) the antibody must pass through the endothelial lining of a capillary or postcapillary venule. The macromolecular permeability of these vessels decreases progressively with increasing molecular weight such that molecules larger than 40 kDa (the molecular weight of IgG is 150 kDa) escape from the plasma only slowly. Smaller antibody fragments, particularly Fv reagents (molecular weight 25 kDa), penetrate the interstitial fluid space more readily than whole IgG. High molecular weight proteins can escape from the microvessels through gaps between adjacent endothelial cells, which are particularly abundant in inflamed tissues. The discontinuous endothelial lining of the sinusoidal circulation of liver, spleen, and bone marrow also allows free passage of macromolecules such as IgG.

BINDING REACTION

The degree to which a therapeutic antibody binds to its target antigen is governed by the concentration of antigen, the concentration of antibody to which it is exposed, the duration of exposure, and the intrinsic properties of antibody and antigen that determine their rates of association and dissociation.

The equation is simple when attempting, for example, to neutralise a circulating toxin. From the known concentration of toxin in plasma and the affinity of the antitoxin antibody the dose required for effective neutralisation can be calculated. For cell surface antigens the analysis is less simple. The concentration of antibody to which the target cells are exposed and the duration of exposure are determined by the rate at which the antibody enters the interstitial fluid and the rate at which it is eliminated from the body. Furthermore, in contrast with soluble target antigens, cell associated targets are effectively multivalent so that affinity is no longer the only factor determining the rate of dissociation of cell bound antibody. Dissociation slows greatly when an IgG molecule is anchored to the target cell surface through both of its antigen binding sites rather than through a single site. Provided the target antigen is expressed at sufficiently high density, bivalent molecules such as intact IgG or F(ab)_2 can bind with much greater avidity than can the smaller univalent Fab and Fv antibody fragments. Complexed antibody may also be taken into the cytoplasm of the target cell, effectively preventing further dissociation. Additionally, a cluster of many cells displaying the same target antigen (a tumour deposit, for example) may behave as an antigen “sink” from which the antibody escapes only very slowly. This is because dissociation of a bound antibody molecule will be followed immediately by rebinding to the same or a neighbouring cell.

ANTIBODY CLEARANCE

Ultimately, all infused antibody will be eliminated from the body. The Fc portion of IgG is thought to determine its catabolic rate, which (in humans) is faster for murine antibodies than for human antibodies. Smaller antibody fragments pass relatively easily from the glomerular capillaries into the renal tubules and are rapidly excreted unchanged in the urine; this greatly shortens their plasma half life. Thus the circulating half life of IgG is measured in days, and that of single chain Fv fragments (scFv) in minutes, while F(ab)_2 and Fab fragments have intermediate half lives.

Clearance of antibody which has been retained in the tissues is slower. Retention of antibodies by tissue due to specific interaction of the antibody with its target antigen is welcome, but non-specific binding to homologous or non-homologous antigens also occurs. Moreover, IgG may be retained in liver, spleen, and bone marrow through the interaction of its Fc portion with Fc receptors on resident macrophages. Fab and F(ab)_2 fragments tend to accumulate in the kidneys.

Persistence of antibodies in normal host tissues may be troublesome, leading, for example, to excessive toxicity of a radiolabelled therapeutic cancer antibody.

For certain applications prolonged or repeated administration of monoclonal antibodies is needed to obtain real clinical benefit. But a host immune response against the infused antibody can greatly shorten its circulating half life. Murine and other non-human antibodies and chimeric antibodies linked to non-human proteins are particularly prone to host responses. For example, a strong human antimouse antibody response can sequester infused mouse antibody to give circulating immune complexes that are rapidly phagocytosed by reticuloendothelial cells, reducing the potency of treatment. This problem can be circumvented by using human or humanised antibodies, although the patient may still mount an immune response against idiotypic (antigen binding site) or allotypic (Fc) determinants of the therapeutic antibody. As a general rule it is preferable to use human or humanised antibodies to rodent antibodies. New methods for screening large human phage antibody libraries will prove useful for this purpose.

Effector mechanisms

When the goal of treatment is neutralisation of a toxin or blockade of a ligand-receptor interaction the therapeutic antibody requires no special effector domain and, depending on the effective valency of the target antigen, should function well as a monovalent (single chain Fv or Fab) or bivalent (F(ab)_2) fragment. More commonly, however, the aim is to destroy a specific target cell. Phagocytosis, antibody dependent cellular cytotoxicity, and complement fixation are the natural effector pathways activated by the Fc portion of cell bound antibody. Murine antibodies do not recruit human effector functions well but this can be completely remedied by chimerisation or by grafting on complementarity determining regions (CDR grafting) to humanise the antibody. Human effector functions are recruited more efficiently by rat antibodies of the IgG2b subclass than by murine antibodies. Smaller antibody fragments without an Fc portion (single chain Fv, Fab, F(ab)_2) can be artificially given alternative effector mechanisms including radioactive metals, plant and bacterial toxins, enzymes, and cytotoxic drugs.

The most suitable effector mechanism depends on several factors. A high density of IgG on the target cell is required to activate complement because it is initiated by crosslinking the Fc portions of two adjacent cell bound antibody molecules. Moreover, Fc mediated recruitment of phagocytes, antibody dependent cellular cytotoxicity, and complement is not possible unless bound antibody stays on the surface of the target cell.

For some conditions it may be more appropriate to use antibodies with artifically linked effector functions. Cells which rapidly internalise bound antibody or
which express the target antigen at low density may be killed more effectively by antibodies conjugated to drugs, toxins, or radionuclides. Radioimmunoconjugates also have the advantage that their radiation can penetrate several cell diameters into the tissues—this may be useful for cancer therapy as the monoclonal antibody cannot penetrate deep into the tumour. The box summarises the available antibody effector mechanisms.

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<th>Effector functions for antibody targeted therapy</th>
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**Clinical use of monoclonal antibodies**

**IMMUNOSUPPRESSION**

Immune responses to self or foreign antigens can lead to autoimmune destruction of tissue or rejection of transplanted organs. Immunosuppressive therapies include corticosteroids, cyclosporin, cytotoxic drugs, and polyclonal antilymphocyte antisera, all of which have high toxicity and are sometimes ineffective. Monoclonal antibodies offer a realistic alternative to these immunosuppressive drugs, and this is perhaps their most useful current application. Potential targets for immunosuppressive monoclonal antibodies include lymphocyte differentiation antigens, cytokines, cytokine receptors, and cell adhesion molecules.

The first monoclonal antibody to be approved for human therapy (OKT3) is an immunosuppressive murine reagent which binds to T lymphocytes and is useful for treating rejection of renal transplants. In common with many other immunosuppressive antilymphocyte monoclonal antibodies it does not stimulate a strong antimesa response. The toxicity of OKT3 is worse with the first dose, which triggers release of cytokines from targeted cells and leads in some cases to hypotension, weight gain, and breathlessness, progressing occasionally to pulmonary oedema. Many other immunosuppressive monoclonal antibodies have been shown to have activity in humans. Among the most promising are antibodies against the lymphocyte antigens CD4, Tac, and CD8 (see below), all of which have now been humanised by CDR grafting, and several monoclonal antibodies which block adhesion of immune and inflammatory cells.

Monoclonal antibodies against CD4 inhibit the function of helper T cells and have been used with varying success to treat acute rejection of renal allografts, rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, psoriasis, relapsing polychondritis, systemic vasculitis, and mycosis fungoides. Tac monoclonal antibodies recognise high affinity interleukin 2 receptors of activated lymphocytes and do not bind to resting lymphocytes. They can therefore block ongoing antigen specific immune responses highly specifically without damaging resting lymphocytes. Murine Tac monoclonal antibodies were shown to prevent early rejection of renal allografts, but antimesa responses were detected in 81% of patients after one month of treatment. Hurn's Tac antibody (TAC-H) was recently compared with the murine antibody in primates given cardiac allografts. The humanised antibody had a longer circulating half-life (103 ± 38 h), was less immunogenic (0% ± 100% antimalabs responses before day 33), and produced a longer graft survival than the murine antibody.

Immunosuppressive monoclonal antibodies will undoubtedly contribute to the therapeutic options against autoimmune disease and rejection of transplants but their precise role has yet to be defined. More detailed understanding of the underlying immunopathogenic mechanisms in many autoimmune conditions and vasculitic states will help future exploration of the therapeutic potential of monoclonal antibodies in these conditions.

**INFECTION**

Agammaglobulinaemic patients suffer from recurrent bacterial sinusopulmonary infection, meningitis, and bacteremia. Viral infections are no more severe in patients with agammaglobulinaemia than in healthy people, suggesting that T cells are the most important initial defence, but lasting immunity is lacking so multiple bouts of chickenpox and measles may occur. These observations suggest that antibodies should be able to prevent bacterial and viral infections. Indeed, regular administration of purified pooled human immunoglobulin provides good protection for patients with agammaglobulinaemia (and hypogammaglobulinaemia or dysgammaglobulinaemia). Polyclonal human immunoglobulin preparations have been used for many years to treat and prevent several viral diseases including hepatitis A and B, chickenpox, measles, and cytomegalovirus infection. Against this background it is surprising that antibacterial and antiviral monoclonal antibodies have been used very little in clinical practice. This may change soon because several antiviral and antibacterial monoclonal antibodies are under development for human trials. For example, humanised versions of monoclonal antibodies to herpes simplex virus and respiratory syncytial virus have been prepared and human antibodies to HIV have been isolated by screening phage libraries. Antiviral monoclonal antibodies can block attachment and penetration of viruses, opsonise virus and virus infected cells for phagocytosis or antibody dependent cytotoxicity, and mediate complement lysis of enveloped virus particles or infected cells. Cocktails of monoclonal antibodies will probably give greater benefit than single reagents.

However, there are important reservations relating to the use of antibodies for treating viral disease. Since T cells and not antibodies seem to be essential for eradicating established viral infections, it can be argued that antibodies are unlikely to be useful in treating these conditions. Moreover, there is evidence that certain viral infections may be enhanced by antiviral antibodies, which can facilitate Fc receptor mediated viral entry into macrophages and some other cells.

**TOXIC STATES**

The use of monoclonal antibodies to treat septic shock has been reviewed recently. Endotoxin, a lipopolysaccharide component of the bacterial cell wall, damages vascular endothelium triggering a cascade of events that leads to septic shock. Because
The target antigen is intravascular IgM monoclonal antibodies can be used. HA-1A, a human IgM antitoxin monoclonal antibody, reduced 28 day mortality by 39% in 105 patients with Gram negative bacteremia. Although the result seems impressive, the antibody is expensive and it is difficult to design protocols that avoid treating large numbers of patients who subsequently prove not to have had Gram negative bacteremia. Moreover, the initial study has been seriously criticized and a second placebo controlled clinical trial of HA-1A has been recommended to determine whether the antibody should be widely used.

Tumour necrosis factor is one of the central mediators of septic shock, and monoclonal antibodies against it are protective in animal models. A phase I clinical trial of one monoclonal antibody against tumour necrosis factor confirmed its safety, but its efficacy has yet to be shown in humans. Besides the obvious examples of tetanus and diphtheria, other toxic states which may be amenable to monoclonal antibody therapy include drug overdosage, chemical poisoning, and snake or spider bites. Already digoxin Fab fragments are well established for the management of digoxin overdose and monoclonal antibodies are being developed for neutralising tricyclic antidepressants.

CANCER (SOLID TUMOURS)

Monoclonal antibodies against cancers have been used for both imaging and treatment. There are numerous possible target antigens, which fall into several broad categories (box). Except in a few cases, unique tumour specific antigens have not been identified, and studies have focused on target antigens that are present to a greater or less degree on some normal host tissues. Examples include oncofetal antigens such as carcinoembryonic antigen and a fetoprotein, epidermal growth factor receptors, carbohydrate antigens, and components of the extracellular matrix such as mucin. Radioimmunoconjugates accumulate in tumour deposits well enough to produce reasonable images, although the image is not yet good enough to seriously challenge conventional imaging methods such as computed tomography. Treatment of cancer with monoclonal antibodies has so far been disappointing. Early studies used immunogenic murine monoclonal antibodies that could not recruit human effector functions. Humanising these monoclonal antibodies or linking them to radiotracers, toxins, and drugs (which may increase immunogenicity) has so far had little impact on their therapeutic efficacy and can produce serious toxicities. However, it would be inappropriate to discount the potential of these alternative killing mechanisms.

An important limiting factor is the inability of infused monoclonal antibodies to reach the target cells. Monoclonal antibodies have good access to the tumour surface as the surface blood vessels of a tumour deposit are relatively leaky to macromolecules but the branches of these vessels which penetrate the tumour parenchyma are not. Once on the surface, however, they meet an impenetrable wall of tumour cells held together by tight intercellular junctions, which makes access to deeper parenchymal regions of the tumour poor. It was hoped that smaller versions of the antibody molecule—for example, Fv, single chain Fv—would escape more readily from penetrating vessels and permeate better through the parenchymal regions of the tumour. However, the early signs are that their lack of avidity (they are univalent) and rapid renal excretion result in lower absolute tumour uptake despite a better tumour to normal tissue ratio.

The toxicity of cancer monoclonal antibodies has been variable. With unmodified murine monoclonal antibodies fever, rigors, nausea, and vomiting are common after the initial doses, immediate hyper-sensitivity reactions can occur, and symptoms secondary to circulating immune complexes are sometimes seen after prolonged treatment. Radioimmunoconjugates usually cause appreciable toxicity to normal bone marrow, and immunotoxins can cause the vascular leak syndrome.

Antibody dependent enzyme prodrug therapy (ADEPT) is a promising research prospect. With this technique an antibody-enzyme conjugate is administered, which localises to tumour deposits. After a few days during which non-specifically bound monoclonal antibody is cleared, an inactive prodrug is administered. The prodrug is converted by monoclonal antibody-linked enzyme in tumour deposits to an active, tumoricidal drug that is small enough to permeate the deeper regions of the tumour. Human and humanised antibodies with improved affinity and specificity are likely to be used increasingly in the future. One recent animal experiment has shown that improved affinity can give improved antitumoral activity. Phage technology could help develop appropriate antibodies. Cocktails of monoclonal antibodies may give better results than single antibodies (see below).

HAEMATOLOGICAL MALIGNANCIES

Monoclonal antibody treatment for haematological malignancies has been more successful than that for solid tumours. Activity against disease in bone marrow, and spleen has been noted, with nodal disease responding less readily. One possible explanation is that the sinusoidal circulations of congestive organs are
easily permeated by immunoglobulins. Also the bone marrow and spleen are rich in host effector cells that can recognise and kill targets coated by monoclonal antibodies.

Murine anti-idiotypic monoclonal antibodies have been raised against unique surface immunoglobulins and T cell receptors expressed respectively on B and T cell malignancies. The results of treatment are encouraging\(^1\)\(^2\) but monoclonal antibodies have to be tailor made for each patient. Alternative targets include a wide array of leucocyte differentiation antigens. B cell malignancies, for example, have been treated with monoclonal antibodies against the lymphocyte antigens CD19, CD22, CD37, and CD52.\(^3\) The monoclonal antibodies are irreversibly degraded by normal lymphocytes, but these are regenerated from stem cells, which are not attacked. Transient antibody related immunosuppression can, however, be troublesome.

Natural effector functions are effective against several haematological malignancies. CAMPATH-1G is a rat IgG2b monoclonal antibody that recruits human complement and antibody dependent cytotoxicity and binds to an antigen (CD52) present on most normal and malignant lymphocytes. Of 29 patients with lymphoid malignancies who received CAMPATH-1G, nine attained complete remissions, although disease in lymph nodes was generally resistant to treatment.\(^4\) A CDR grafted version of this antibody (CAMPATH-1H) was the first humanised monoclonal antibody to enter clinical trials and induced complete remissions in two patients with B cell non-Hodgkin’s lymphoma, one with lymph node disease.\(^5\) More extensive clinical testing of CAMPATH-1H is currently under way.

Immunotoxins and radioimmunon conjugates have shown activity against lymphoma but direct comparisons of alternative effector mechanisms on a single monoclonal antibody have not yet been made. Polyclonal antiferritin antisera have been shown to target Hodgkin’s disease deposits more efficiently than antiferritin monoclonal antibodies,\(^6\) which suggests again that monoclonal antibody cocktails may be the best way forward.

**Other applications**

Monoclonal antibodies are being developed for imaging of infected myocardium (antimyosin), deep venous or arterial thromboses (antithrombin), and foci of infection of inflammation. Antithues monoclonal antibodies have been made for treating rheus haemolytic disease and antiplatelet monoclonal antibodies for prevention of intravascular thrombosis. Monoclonal antibody enzyme conjugates targeted at blood clots are also under development as novel fibrinolytic reagents.

**Conclusions**

We have progressed considerably since the early days of monoclonal antibody therapy but there is still much to learn. Human (or humanised) monoclonal antibodies are preferable to rodent monoclonal antibodies for most applications. Cocktails of monoclonal antibodies should be more effective than single antibodies and production of such cocktails will be helped by the advent of human phage antibody libraries. Enhancements of an antibody’s affinity is now possible by phage technology,\(^7\) and the early signs suggest that it should improve therapeutic efficacy. Definitive studies comparing the clinical efficacy of various natural and artificial effector functions are needed, and there is scope for boosting natural effector mechanisms with lymphokine therapy. For the future antibodies and antibody genes may be used increasingly to redirect cytotoxic cells or for targeted delivery of genes and other drugs wrapped up in viruses or liposomes.
Sir NORMAN JEFFCOATE
MD, FRCS ED, FRCOG

Norman Jeffcoat was a student, protégé, and disciple of Professor William Blair Bell, the founder and first president of the College of Obstetricians and Gynaecologists. His career progress was rapid; he was appointed to the first whole time chair in obstetrics and gynaecology in the University of Liverpool in 1945.

He was a wonderful teacher and a great supporter of the undergraduates. They received superb tuition in all the basic skills of the two disciplines from a man whose meticulous attention to history, detail, and physical signs never allowed issues and principles to be clouded. He had an uncanny ability to bring on postgraduates at the appropriate pace, involving them in research projects at just the right time. His main work, Principles of Gynaecology, was first published in 1957 and is now in its fifth edition and remains a classic. It has given generations of aspiring obstetrician-gynaecologists a wealth of knowledge presented with great clarity in an uncomplicated style. Understandably, he was in great demand worldwide: he gave more than 500 guest lectures and orations and was a visiting professor at eight universities.

The Gynaecological Visiting Society started by Blair Bell had an important role in the foundation of the College of Obstetricians and Gynaecologists, and Professor Jeffcoate was its convenor for seven years. Thus an institution in the college was as natural as his becoming its president in 1969; his influence at the college was immense and he worked tirelessly for it, never missing the chance to promote it and its ideals among his charges. After his retirement he withdrew from all professional activities, though he maintained a keen interest in college affairs.

As with many great men, he had other talents. He was accomplished at both rugby football and cricket, an artist (in watercolours), and, with his wife, Josephine, who died in 1981, a warm and welcoming host. He and Josephine had four sons, one of whom is a professor of endocrinology and one a consultant physician.

Friends and colleagues will miss his wisdom, breadth-taking long term memory, loyal support, and friendship. His contribution to obstetrics and gynaecology was immeasurable.

T A Jeffcoate


S HEROLD MRCPSYCH

Throughout her training Sigrid Herold maintained an interest in research, making a valuable contribution to positron emission tomography and specialising in its application to autism, schizophrenia, and cerebrovascular disease. Most recently her research also encompassed psychosocial and epidemiological aspects of schizophrenia. Her critical mind and practical research abilities were enhanced by the clarity, enthusiasm, and sense of humour with which she communicated. She believed strongly in the value of good teaching in medicine and facilitated a high standard of postgraduate psychiatric training at St Bernard’s Wing, Ealing Hospital.

Outside work Sigrid delighted in being with her family. Her openness to affection and generous nature were always evident. Her interest in art and social issues and her good cooking gave rise to enjoyable hospitality. She successfully married a busy and fulfilling work and home life, and through her experience she offered support to other women doctors who knew her. She died of cholangiocarcinoma and is survived by her husband, Terry Jones, and 4 year old daughter, Julia.

Barley Randle was a pioneer of physical medicine and particularly concerned with rehabilitating patients with neurological conditions, including stroke and head injury. He was especially able in helping patients to come to terms with their problem and make the best of it.

Barley found no difficulty in coordinating a team of consultants, general practitioners, clinical psychologists, speech and occupational therapists, and physiotherapists. In 1966, as a result of his efforts, the first employment rehabilitation centre based in a hospital was established at Garston Manor. It was run by the Department of Employment with shared medical facilities, the aim being to assess patients for work or vocational training while they had medical treatment. It proved a great success. In 1972 Barley moved to Cambridge to open a new rehabilitation centre at Addenbrooke’s Hospital. When the unit opened in 1976, after delays and setbacks, it was not entirely to Barley’s satisfaction, but it became a demonstration centre.

Barley was a warm, cultured man with a puckish sense of humour who got on well with people. I suspect that his interest in people dictated his resignation from the NHS in 1979 and appointment as medical director of the Papworth-Enham trusts. These charitable trusts were designed to promote work skills by providing assessment, training, housing, and jobs in a village setting.

In 1986 he retired to Brighton. Sadly, in 1990 he developed a disorder that fell within his own specialty.