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LESSONS FROM A SYMPOSIUM ON ONCOLOGY HELD IN THE COLLEGE ON 13 APRIL 1994*

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Changes in the management of breast cancer (Dr I. E. Smith; see p. 56)
The management of breast cancer has undergone a revolution in the last century, as our understanding of the pathology and biology has developed. Clinical studies have shown that Halsted's radical local treatment does not influence survival, since there are often micrometastases at the time of presentation. Hence, the move towards conservative surgery, local radiotherapy, and hormonal and chemotherapy to reduce the chance of relapse and to improve survival.

The move towards neo-adjuvant treatment seems logical for larger primaries, allowing conservative surgery and an opportunity to study disease response *in vivo*. The first study at the Royal Marsden Hospital in 1986, and similar studies since, have shown response rates of around 70% in the primary tumour using various drugs. More effective regimes, and longer periods of follow up are needed. At the speaker's institution a regime comprising cisplatin, epirubicin, and prolonged infusion of 5-fluorouracil (5-FU) is under study. Most patients have undergone conservative surgery (64%) or trucut biopsy alone (29%). Over 18 months few have experienced local relapse. Survival figures are awaited. Complete pathological responses rates may be as high as 28% in the primary tumours and 61% in the nodes. The effects on tumour cellularity and marker expression are being investigated.

Adjuvant therapy for colorectal cancer (Mr R. G. Gray)
Colorectal cancer claims over 20,000 lives in the UK each year, so that even small advances in prevention, detection, and adjuvant treatment might save many lives.

An overview of published and unpublished data on the use of chemotherapy sought to reduce publication bias and random errors, and to provide some indication of the benefits of treatment.

In 1979 a small study of portal venous infusion of 5-FU showed responses in patients with hepatic metastases. Subsequently, survival benefit at 3 years was demonstrated in two studies in the adjuvant setting, but another study showed no significant effect. Reduction in the odds of death from the disease may be 16% at <60 years, 21% at 61–69 years, and 19% at >70 years.

Prolonged adjuvant 5-FU and levamisole reduced relapse rates over a period of 7 years and was recommended as standard treatment for Duke's stage C in the USA. However, no patients were given 5-FU alone. Results from about 19 studies suggest reductions in the odds of death of 15% (2–26%) for 5-FU alone, and 15% (6–24%) for 5-FU-based combinations. Studies combining 5-FU with

*A list of speakers and the titles of their papers presented at this symposium is recorded in *Proceedings* Vol. 24 p. 475.

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folinic acid have shown a 10–15% reduction in 3 year relapse rates but a less obvious survival benefit.

About 40% of clinicians in the UK do not offer adjuvant treatment and the evidence suggests a change in practice may be justified.

Intensive therapy for malignant disease (Professor J. O. Armitage; see p. 50)
Can we take advantage of a dose-response effect, and is it worthwhile?

In the face of increasing dose, response rates eventually reach a plateau and non-haematological toxicities increase. Overcoming bone marrow toxicity is possible using bone marrow transplants (BMT), stem-cell harvesting and growth factors. Mortality following autologous BMT (ABMT) has decreased from 40% to 1%. In the USA, the majority of patients undergoing transplantation have breast cancer. In the UK, leukaemia and lymphoma remain the main indications. Disadvantages of ABMT include reinfusion of malignant cells, graft versus host disease, infection, cost, and the induction of drug resistance.

Administration of higher doses should be justified. Ten per cent of patients with advanced leukaemia who undergo allogeneic transplant survive. About 15% of patients with 'resistant' lymphoma can be cured by dose escalation with ABMT. The most suitable candidates are younger, fitter patients with less advanced disease. Growth factors alone can shorten marrow recovery time, efficacy depending on the quality of stem cells. Stem cell harvesting may ultimately reduce the need for ABMT.

Quality of life (Professor J. F. Smyth)
The search for curative treatment is an important goal, but it is also essential to maintain quality of life (QOL) particularly if cure is not possible. Assessment of QOL has not proved easy. Advances in modification of toxicity have reduced the side effects of palliative chemotherapy. Better understanding of emetogenesis has led to the rapid development and use of 5HT-3 receptor antagonists. Haemopoietic growth factors have made a smaller contribution by reducing periods of neutropenia associated with hospitalisation.

QOL depends on psychological, social and physiological functioning. The *general health questionnaire*, the *sickness impact profile*, and the *hospital anxiety and depression scale* have been used to assess QOL. The *Rotterdam symptom checklist*, and the *European Organisation for Research into Cancer* (EORTC) *questionnaire* are designed for use in oncology. The latter takes 10–15 minutes to complete and has been used in breast cancer trials. Unless assessment of QOL is identified as a main objective in a trial it can easily be neglected. QOL studies should be adequately funded, employ key personnel, and produce accurate results.

Palliative care (Professor G. W. Hanks)
Palliative care was born out of the hospice movement. St Christopher's Hospice opened in London in 1967 and in 1992 the Hospice Directory listed almost 180 hospices and 160 hospital support teams. Their aim is 'to provide active total care of patients and their families by a multi-professional team when the patient's disease is no longer curable' (WHO 1990). Palliative care became a separate medical specialty in the UK in 1987, and the number of consultants is increasing. Research has been done on pain control, morphine pharmacology, transdermal phentanyl, and the management of intestinal obstruction in terminal disease.

There are now a number of specialist journals. It is proposed that palliative care should be an integral part of training for all physicians.

More than two-thirds of patients require palliative care at some stage. This should ideally run in parallel with active care, resources being appropriately distributed at each stage. Twenty per cent of patients still die without access to a hospice. Improvements will not be effected simply by increasing the number of hospices. More community and hospital based teams are needed. Appropriate, early referral of patients will ensure that increasing numbers benefit from this important service.

Hodgkin's Disease: the road to a cure; (Professor D. C. Linch)

Radiotherapy and combination chemotherapy led to major advances in the 1940s and 1960s. Progress has subsequently slowed. In localised disease, response rate but not overall survival, has improved. In advanced disease, treatment with MOPP (mustine vincristin (Oncovin), procarbazine, prednisolone) resulted in 50% survival at 10 years. Alternating MOPP with ABVD (adriamycin, bleomycin, vinblastine and dacarbazine (5-(3,3-dimethyl-1-tri-azeno)-imidazole-4-carboxamide) significantly improved survival. Other alternating regimes have not proved superior. The exact role of radiotherapy remains unclear, although it is generally agreed that bulk mediastinal disease should be irradiated.

Some patients may do better with intensive induction therapy followed by ABMT. Poor prognostic factors at presentation include bulk disease, lymphopenia, anaemia, and low albumin. Although it has been possible to achieve complete responses, mature survival data from ongoing studies is awaited. Patients who fail to achieve complete response with standard therapy, who relapse within a year, or who fail two regimes, may also respond to dose intensification. Since the early 1980s ABMT has improved survival by >20% in relapsed disease, with procedural mortality rates falling from 10 to 3%. Growth factors combined with ABMT confer no survival advantage, only marginally improving marrow recovery. Peripheral blood stem cell harvesting may prove more useful, but its role is not yet defined.

A simple calculation suggests that the use of ABMT in first line treatment may not be necessary. If 85 of 100 patients are given standard chemotherapy (15 being unfit), about 35 will achieve only a partial response. Of the 50 achieving complete response about 15 will relapse. Fifty patients will thus be suitable for ABMT, of which about 25 will achieve complete response. If the same 85 patients are given an ABMT initially, the complete response rate is similar at 65 to 70%. Perhaps, therefore, the way forward is to focus on small improvements in second line treatment rather than dose intensification.

Developments in cancer therapy (Professor G. P. Canellos)

Many cancers remain incurable despite advances in combined modality treatment. Current research into drug resistance, growth factors, genetics and tumour biology may explain the failure and provide new therapeutic options. Recently interest has been focused on gene therapy, the divergent aims of which are to restore biological normality or instil 'suicidal genes'. Methods for gene transfer include lipofection, electroporation, and viral vectors (e.g. DNA tumour viruses such as herpes simplex virus (HSV) and non-pathogenic retroviruses). Potentially

useful genes include immune-modulation genes such as interleukins and granulocyte macrophage colony stimulating factor (GMCSF), hrowth regulatory genes (e.g. P.53) and retinoblastoma gene, and cytotoxic genes such as tumour necrosis factor (TNF).

Brain tumours provide a good model: the normal cells are not actively dividing, HSV is neutropic, and local infiltration, vector delivery techniques and uptake potentiators are available. Cytotoxic genes have been instilled: the TNF gene; the thymidine kinase gene, allowing local conversion of gancyclovir to a cytotoxic agent; and the cytosine deaminase gene which similarly allows conversion of 5-fluorcytosine to 5-FU. An 'innocent bystander' effect is observed due to inter-cellular contacts, messages, and exchange of genetic material. Introduction of the multi-drug resistance gene into haemopoietic stem cells could enable them to withstand dose intensification. Transfer of the TNF gene into autologous breast cancer cells and subsequent reinfusion could result in tumour cell kill by immune stimulation. GMCSF also increases tumour antigenicity. The P53 gene is mutated in 30–60% of all high grade gliomas. Introduction of the normal gene could restore normal growth. Other mutated tumour suppressor genes could be targeted.

In anti-oncogene therapy, antisense nucleotides are introduced which 'switch off' the oncogene. Studies have been done in experimental systems and in Philadelphia chromosome positive chronic myeloid leukaemia. Antibody directed therapy has been tried in lymphoma using antibodies directed against T or B cell markers (e.g. CE20 or B1) linked to complement, natural killer cells, toxins (e.g. ricin, pseudomonal, diphtherial), and radionuclides (e.g. I131, yttrium, caesium); such complexes will bind normal T and B cells and at other unwanted sites. Heterogeneity of tumour antigen expression, resistance, the development of human anti-ricin antibodies or human anti-mouse antibodies and poor tumour blood flow present problems.

Paracrine angiogenic proteins allow tumour neovascularisation. Experimental agents against neovascularisation are being studied in brain tumours. Although time did not allow a comprehensive review of all areas of research, the talk did bring into sharper focus the areas where breakthroughs in cancer treatment may be made.

For debate: the cost-effectiveness of cancer therapy (Mr D. K. Whynes, health economist; see p. 67 and Professor B. W. Hancock, clinician; see p. 61)

If the success of the NHS is viewed in financial terms, it might be concluded that the last 30 years have been ones of achievement. Hospital through-put and health care spending has increased and waiting lists reduced.

Government spending on cancer care accounts for about 7% of the total health budget, which seems low considering that 25% of the population die of cancer. However, funding also comes from the general public and recognised charities. Appropriate allocation of funds is important, and suitable ways of analysis cost-effectiveness are needed.

The health economist sees medical care as a process involving resource input (cost), intervention, and outcome. Costs can be direct (e.g. cost of drug and hospital care), indirect (e.g. to relatives and society), or intangible (e.g. reduced QOL). In oncology, outcome can be measured in terms of survival and QOL, as well as reduced cost to society and carers. Perhaps the simplest direct measure-

ment is the 'quality benefit year cost'. For young patients with curable malignancies it is easier to calculate and lower (e.g. £500/year for a patient with metastatic teratoma receiving chemotherapy). For palliative therapy cost is more difficult to determine and is higher. For adjuvant therapy, which may not benefit all patients, it is also higher (e.g. £4,000/year for a patient with breast cancer and £1,700/year for a patient with colorectal cancer). In all cases where treatment benefit is not clear, attempts should be made to enter patients into clinical trials.

Clinicians should work with health economists to undertake the difficult task of cost-effectiveness analysis. Such analysis should provide a framework for standard practice, but the individual needs of the patient should not be compromised by purely financial constraints, and cost-effectiveness should not become a euphemism for cost-cutting.

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IMPROVING CLINICAL QUALITY IN THE HEALTH SERVICE

AN OUTCOMES SYMPOSIUM HELD IN THE COLLEGE ON 29 APRIL 1993

The quality of medical care can be assessed by looking at the results or, in audit terminology, outcomes. The College together with Lothian Health, the health services organisation for the Lothians, organised a symposium on the outcomes of medical care in April 1993. The programme was devised by Dr Sheena Parker of Lothian Health and the meeting was organised by Dr J. Petrie and Christina Pottinger of the Education, Audit and Research Department, RCPE. Funding was provided by the Clinical Resource Audit Group (CRAG) of the Scottish Home & Health Department and Glaxo Pharmaceuticals (UK) Ltd. Around 100 participants attended during a day characterised by lively questioning and debate.

EXECUTIVE SUMMARY

Clinical outcomes are measured changes in the health status of individuals or groups which can be largely attributed to interventions by the Health Service. Measurements of the effectiveness of clinical care need to be *valid and simple*, so that they can be achieved as part of routine practice, and *repeatable* so that changes in health status can be measured over a period of time. Clinical outcomes can only be compared between service providers if the facilities for care, the patient population and staff skills are broadly equivalent.

The lead should be taken by CRAG and the Scottish Royal Colleges in developing national clinical guidelines incorporating outcome measures which can be shown to change clinical practice and be capable of audit. The Colleges should work with purchasing authorities and the profession to develop guidelines centred on patients and aimed at achieving the best outcomes in the context of the NHS in Scotland. The guidelines should ensure that:

Local protocols are developed from national guidelines that can improve the outcome of care for patients and the training of clinical staff.
Purchasing authorities work together with the profession in their areas to develop clinical outcome measures useful to both clinical staff and purchasers in monitoring the effectiveness of clinical care.
Recognising that patients' views on the quality of care are potentially valuable and should be taken fully into account both by purchasing authorities and clinicians.
Information arising out of medical audit should be shared with the public and with the purchasing authorities which have a role as patient advocates.
The development of shared care between the primary and secondary sectors is evaluated in terms of the impact on clinical outcome as well as on cost.
More use is made of available data to compare clinical outcomes and encourage the development of information networks between the providers of care to minimise differences in outcome.