Reviews in Medicine

Palliative medicine

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Introduction

This article provides an overview of palliative medicine. The approach is slightly oblique by seeking to examine the philosophy of care and apply it to aspects of management, both clinically and with respect to service delivery. Review articles and source material are listed with the subheadings that consider aspects of the specialty or practice.

Background and philosophy^{1,2}

Definition

To 'palliate' comes from the latin *palliare*, to 'cloak'. It has been used figuratively to mean to disguise or hide. In medicine it was used first in the 16th century to describe the alleviation or mitigation of suffering.³ At first sight, palliation may simply be seen as the laudable desire to alleviate patients from the most distressing symptoms of the dying process. However, to equate palliative medicine merely with the therapeutics of symptom control is truly simplistic. Hence, in the hospice movement, palliation has traditionally referred to the management of patients 'in whom death is almost certain and not too far off, where the control of symptoms is the prime clinical objective ... (and) the emotional and spiritual preparation of both patients and "family" is given high priority'.⁴ The European Society of Palliative Care defines it as follows: 'The provision of active total care when disease is not responsive to curative treatment. Palliative care neither hastens nor postpones death; provides relief from pain and other distressing symptoms; integrates the psychological and spiritual aspects of care, and offers a support system to help the family cope during the patient's illness and in bereavement'.⁵

Clearly patients with chronic, non-fatal disease and indeed those with acute, highly symptomatic disease such as postoperative pain will also benefit from specialist advice on symptom control and

may benefit from short-term referral to palliative services. Whilst recognizing this and preferring a broader definition of palliative care, this article will concentrate more on the care of the dying.

Its basis

Fundamentally, two things separate the concepts of palliative medicine from some other branches of medicine: the primary clinical aim is not to cure, but to relieve suffering, where symptoms, the disease process and its manifestations are seen actively within the wider context of the person. Either cure is impossible or potentially curative treatments may be seen as unsuitable because of pre-existing or unacceptable iatrogenic morbidity. In short, there is a shift in the balance between quantity of life in the direction of the quality of life for a group of people, not with a normal life in view, but rather a peaceful, appropriate and dignified death. Secondly, the life remaining to a patient whose death is impending is precious, and the importance of wider issues and patient centred care appears all the more vital.

Regardless of what is taught about holistic practice, clinicians still place medical decision making with the doctor; where criteria such as pathology, prognostic indicators, or objective side effects (that is, iatrogenic disease, such as marrow suppression) take precedence. In contrast, palliative philosophy considers quality of life or a patient's plans and objectives as the more appropriate foci of decision making. Hence, whilst applying scientific rigour to practice and without denying the relevance of nosology, in debating the benefit of a planned intervention, the *possibility* of an increased median survival or reduced long-term morbidity may be overridden by the *certainty* of valuable time 'wasted' in hospital or of some immediate cosmetic or social consequence when short-term benefit is the order of the day.

Dunstan sees the backdrop of palliative medicine to be an inevitable 'mortal end ... with the minimum of distress and the maximum capacity to enjoy or

even repair human relationships as s/he might choose. Thus the management of a patient at one time may be to maintain quantity and quality of life with aggressive management, and following resolution of issues, a time may come where medication administered for the control of distress ... (may) ... putatively speed up the patient's death'.⁶

The physician's role within palliation is therefore broad and as much that of informant, advocate and facilitator as diagnostician or decision maker. Without indulging in polemic, palliative medicine should represent what is truly good clinical practice – evaluation of all investigations, procedures and treatments in terms of their cost/benefit to the patient.⁷ Care is consciously patient centred in a way that is sometimes forgotten in hospital practice and, although the pursuit of scientific excellence is essential and commendable, it must allow for the individuality of its only real justification, its patients.

Thompson, for example, maintains that in the context of terminal care, this incorporates the patient's human right to be involved in decision making – his or her right to decline medication and investigation on the one hand, and the right to treatment and care on the other.⁸ Clearly, this may ultimately mean the right to a good death with dignity or grace with psychological, practical and spiritual support as well as the best clinical care. Nevertheless, in fulfilling these requirements, palliation is rather more than simply 'settling for comfort', by active seeking of the means by which integration can finally occur, using whatever technology and expertise is necessary.⁹ Fundamental to palliative medicine is a sharing of the responsibility for maintaining the rights of patients, their loved ones and the professionals involved, within a framework of true multidisciplinary care.¹⁰

Failure of cure in the context of a fatal disease process presents particular difficulties for the patients facing the unknown¹¹ and for professionals who may feel they have failed.¹² This attitude amongst professionals is understandable given the nature of modern medicine. However, it must change.¹³ Particular professional skills are therefore needed for work in this field.^{14,15}

Its extent

Care of those dying with cancer is currently the fulcrum of the work of palliative medicine. With 22% of deaths in Europe being related to cancer, 60% of cancer patients in developed countries dying of their disease, and an estimated 50% increase of malignant neoplasms in the next quarter century, aside from the AIDS pandemic, there is no shortage of need for the skill of the palliative physician.^{16–18} In terms of outcome, it is recognized that on presentation about 55% of cancer patients

have incurable disease and that following curative strategies, a further 15% will move from the curative to the palliative arm, leaving only 30% in the group of long-term cure.¹⁹ In other words, 70% of people with cancer will require terminal care and the role for an expert in palliation is increasingly acknowledged alongside the oncologist, surgeon or radiotherapist.^{20,21}

In the UK, palliative medicine has developed as a distinctive discipline only over the last 30 years.²² It is now well defined with a clear philosophy of care, its own association²³ and an increasing literature. In 1987 it was recognized as a specialty by the Royal College of Physicians, and guidelines have been debated and are now set for higher medical training and accreditation in the field with a projection of about four to six new consultant appointments per year,^{15,19,21,24–26} together with appeals that the undergraduate curriculum should contain teaching on the care of the dying.^{13,27} In response, the Association of Palliative Medicine has published a curriculum for students, general professional and higher specialist training.²⁸ The Department of Health requests that all Health Authorities review their services for the dying; planning teams exist now in many authorities.^{14,29}

From its beginnings with an emphasis on cancer, palliative medicine has now developed and extended expertise in symptom control and alleviation of suffering of the dying in a range of different contexts, both inside and outside hospices. The infrastructure has burgeoned, not least because of the initiative of voluntary organizations. By the beginning of 1992 there were 470 hospice services in operation within the UK and Ireland. This includes 178 in-patient units providing almost 2,900 beds, 186 day care facilities, 360 home care teams working from hospices, hospitals, or independent community bases, and over 160 hospitals with support teams or clinical nurse specialists.³⁰ This is still quite insufficient provision, as only about 10% of dying patients receive specialist support and about 2% die in a hospice.

Hospital-based palliative services are beginning to spread and advise more specialties within general hospital practice. The first amongst these was begun at St Thomas' in 1977.³¹ Most teams are multidisciplinary and inexpensive to run,³² though not without their problems,³³ and some hospitals have palliative or continuing care units 'in house' for the dying.³⁴

However, whilst it is recognized that about 2% of dying patients will be cared for in a hospice and 50–60% will die in hospital,^{20,35} a majority of patients express a desire to die at home^{36–38} and the Wilkes Report on national terminal care policy recommended that developments in terminal care should be based mainly in the area of domiciliary care.^{14,39}

Its implementation

The models and strategies of care of the dying are many and varied, and are specific to the particular needs of the locality and the integration and structure of the clinical service in terms of hospital and local hospice residential facilities. The nature of the service that develops is therefore entirely dependent upon responding to these individual needs. However, one thing is paramount in palliative care, and that is multidisciplinary practice.¹⁰ To say that this is easy would be wrong since the professional base from which each discipline comes carries with it certain preconceptions and these do not necessarily correspond with those coming from other disciplines.^{40,41} Tensions, prejudices and 'clashes of culture' if left unaddressed can have unfortunate consequences.³³

However, no single person or discipline can encompass the skills required for adequate and holistic care of the dying, and this needs to be acknowledged. Cicely Saunders likens the multidisciplinary team to a collage comprising all the different professionals involved in the total care of the patient. For the needs of the patient and family to be met adequately, there is no option other than multidisciplinary care, and the challenge to us all is to provide mechanisms and vehicles for effective development and integration of such services.

Of particular importance is the acknowledgement of all concerned that the common aim is to provide an adequate, effective and targeted service

to meet the needs of the individual, and that issues of practice are of relevance within a framework of equity and not hierarchy. In areas, therefore, where services are about to be developed, these elements need to be incorporated, and the service should be established with mechanisms in place for personal support and team facilitation, so that the early phases of building a service are as painless and as productive as possible.

The multidisciplinary team is the beginning of an answer to the rather ambitious stated aims of palliative medicine. Pooling of resources and recognition of the importance of the function of each individual of the team is the key to effective multidisciplinary teamwork. Such an approach also has the advantage of shared expertise and mutual support in what is well recognized to be a potentially very stressful area, taking its toll of morbidity amongst professionals. This is acknowledged by the recommendations of the Royal College Working party on Standards⁴² (Table I).

Management strategy

Clinical cost–benefit and the therapeutic ratio^{7,43}

Clinical decision making and planning is much more difficult when it is clear that the patient will die regardless of one's therapeutic endeavour. Acting 'in the patient's best interest' can no longer be justified by following clinical algorithms

Figure 1 Applying a therapeutic index or balancing cost and benefit may be expressed visually with a beam balancing curative (pathology based) and palliative (symptom based) options on the fulcrum of the patient's agenda items. This visual representation is simple and practical. Regular review is vital, and in the process of evaluation and planning, this should be done weekly, as views may change radically.⁴³

Table I Standards for palliative care

1. Statement of values and objectives related to the care of dying is available to the staff as a guide for planning, providing and evaluating service
2. Written and updated policies reflect current knowledge and principles of care and are consistent with that of purchasing and providing and registering authorities
3. Service provision and clinical practices, wherever possible, should be based on research evidence and the demonstrable needs of the community
4. Services are planned to allow the population appropriate and equitable access to care
5. Staff education and development reflects the level of activity and practice of the different disciplines
6. The direct patient contact of primary care will be assessed, planned, implemented and evaluated by professional staff with competence, compassion and sensitivity to the particular needs of the dying person and his or her family
7. The well-being of patient, family and staff is promoted by a positive approach which enables them to identify and use appropriate coping strategies
8. The caring team offers a range of skills to meet the particular needs of the patient and family
9. Specific contributions of different disciplines to patient care are valued and used to maximum effect
10. A high standard of palliative care is facilitated by the development of a specific quality assurance programme

Palliative care is defined here as 'palliative care for people with terminal illness' and rests on an acceptance of dignified death and a focus on the psychological and social needs of the patient and his/her family. Such an approach enables the needs of patients with a diversity of diagnosed illnesses and from a range of ages to be embraced.

alone.^{44,45} This is made all the more difficult in the light of studies such as that of Slevin *et al.*⁴⁶, who found that, despite palliative care workers' reservations about the use of radical chemotherapy when the likely benefit is small, they may be at odds with the patients. The study of 100 patients, 100 controls and a variety of professionals showed the median benefit needed to make radical treatment worthwhile to the patient might be as low as 1% chance of cure, a prolongation of life of 12 months and a 10% chance of relieving symptoms. The patients were significantly more likely to agree to treatment with small chance of benefit than the controls or the professionals.

The most appropriate approach therefore is to shift the balance of decision making in the direction of the patient and to balance strategies around their agendas, rather than the clinical indices which we use under normal circumstances.^{9,47,48} This is addressed head on within an ethical framework by Ashby and Stoffell using what they call a thera-

peutic ratio⁷ which examines the balance of active versus palliative care and the cut-off points that we apply, not only with respect to cancer, but also to things such as dialysis, ventilation or feeding. The concept of risk-benefit analysis is established in pharmacology and oncology, relating toxicity, morbidity or mortality to benefit (measured in a variety of ways).⁴⁹

With respect to palliative care, Ashby and Stoffell define with their model three categories. *Curative* – the stage of therapeutic intervention within a disease's natural history where cure or complete remission is a realistic expectation and therefore where management is dictated explicitly by the disease process. *Palliative* – the stage of partial response where no prolongation of life is expected, or where the balance of time benefit versus time spent or intensity of therapy is unfavourable. Endeavours are now directed at quality and comfort with a lower tolerance to the potential cost of therapeutic modalities. *Terminal* – the phase when the physical shutdown, debility and anticipatory grief is actively under way, is a time where no treatment-related toxicity is acceptable.

The uncertainty of transition between phases is probably seen most starkly in late stage human immunodeficiency virus (HIV) infection and in the young with malignancy, where the delicacy of a balance rather than clear phases, makes the notions of uncertainty and flexibility more appropriate (Figure 1). Acknowledgements of the patient's understanding of their disease, the future, their methods of coping with bad news and uncertainty, and their central role in decision making is fundamental. A clear view of the individual's family, both 'biological' and 'social', and its role in decision making is equally important.⁵⁰ Multidisciplinary care cannot be overemphasized in helping patients through these difficult transitions when the priest, social worker, psychologist, or trusted friend may have the most constructive contributions to make.^{51–53}

Auditing the therapeutic ratio – quality of life⁵⁴

Having argued for a wider view of clinical management in the light of the dying patient, one is faced with the challenge of measuring the effectiveness of such practice for two reasons. The first is obvious and important, namely, that a pragmatic and supposedly patient-centred approach, where disease is allowed to progress, must provide tangible benefit for its justification. The second is arguably more important but rather disturbing. In a Health Service where free market economics are being applied to a finite purse, clinical cost-benefit of management in favour of patients will have to be justified in terms of financial cost-benefit as

well.^{55,56} To protect the patient, it is therefore imperative that clinical care incorporates some objective assessment of quality of life as distinct from quality assurance.

A number of effective, simple tools are available^{57–63} for measurement of quality of life, although better audit systems have also been developed to incorporate aspects of relationship, communication and professional effectiveness as well as symptom control and patient satisfaction.^{64–66} Fortunately this is an area of active research at present and in the future our techniques will improve.

Issues of clinical practice

Symptomatology and its meaning

The generic definition of symptom, in the pathological sense, is 'a phenomenon or circumstance accompanying some condition, process, feeling, etc. and serving as evidence of it'.⁷³ However, for the clinician, it is in many respects some distance from the underlying process. The brain receives information, generated either peripherally or centrally, that 'something is wrong', it is registered, identified, quantified, compared with a personal, historical database of identical or similar stimuli, from which its 'objective' significance is derived (for example, 'I am breathless, but I have climbed the stairs'). It is then interpreted and a meaning put upon it (for example, 'nevertheless, I am more breathless than usual. I may just be unfit, but the doctor said . . .'). For the athlete, breathlessness is, in a sense, a tool; for a hyperventilator it is a somatization, but for someone with progressive, fatal disease it could mean either nothing, or that death is not far off.

We must not underestimate the effect that information can have upon a patient.⁵⁰ The aside that a certain symptom may mean disease progression is judged by us according to additional history, objective examination or judicious investigation. These luxuries are not available to the average patient so that their interpretation as to meaning will be limited and the more open to influence by mood and fears.⁶⁷ The solution is not to withhold information but to give time to explanation and careful discussion of the future in the light of both pathology and psychology, and meaning in its broadest sense.⁶⁸

Two things need emphasizing: that any symptom, however generated, is a genuine symptom and that one should always assume that there is a physical trigger, until proven otherwise.

Three areas will be considered in the following sections: the *palliative approach* with respect to three symptomatology; pain, breathlessness, and

problems relating to the gut; the *palliative–therapeutic interface* as exemplified by late stage HIV disease and some of the invasive procedures that are relevant to cancer; and the *terminal phase*, with particular reference to the last 48 hours of life.

The palliative approach

Despite the diversity of symptoms that cause distress, pain remains the major concern of patient and professional alike. Not surprisingly, it was the earliest focus of attention for research since when the area has developed considerably.

Pain – the paradigm of palliative medicine^{67,69,70}

Pain control is addressed by virtually all reviews of palliation, not because it is the only horse that we can flog, but because understanding of its management, and in particular of the use of opiates remains poor within broad-based practice. It also exemplifies the palliative approach in all its dimensions. Whilst cancer pain is experienced by about 1/3 of patients, it is much more common in advanced disease, reported in between 70–90% of patients.⁷¹ Figures in the region of 70% are also reported in HIV^{72–74} and 64% for motor neurone disease.⁷⁵ Taking chronic disease overall, pain is reported in about 65%. Fortunately, the majority of patients can be helped by simple drug therapies and 60–80% of patients with cancer pain will be controlled with oral medication.⁷⁶ A World Health Organisation survey of 1,200 patients with cancer and pain showed 86% to be rendered pain free, 11% to have acceptable relief, with only 3% experiencing partial relief.⁷⁷

Mechanisms and meaning

Nociception is the mechanism and the pathophysiology of pain consequent upon tissue damage and neurotransmission. Pain (as reported by the patient) would be the end product of nociception, neuropathic mechanisms and the psychological perception of the individual.

Pain finds its etymological root in the latin *paena* ('penalty' or 'punishment').³ Not surprisingly, therefore, the significance of pain to the individual and professional alike relates not just to the obvious distress and unpleasantness of the sensation but to deeper issues. This is broader than nociception as it may be reported in the absence of the tissue damage and precipitated, for example, by family stress,⁷⁸ psychological factors⁷⁹ or spiritual dilemmas.⁸⁰ Davidson in his review, for example, points out that in asking questions about pain and mobility often we avoid the real questions about life and death, and is blunt in asking then how can

we see the meaning of pain outside the negative or evil.⁸¹

However, virtually all cancer patients with appropriate history and investigation will be found to have one or more physical precipitants.⁸² It is important, for example, to identify as early as possible specifically remediable lesions responsive to radiotherapy,⁸³ or more specific approaches. Portenoy in his excellent, brief review of the aetiology of cancer pain⁸⁴ draws this distinction between nociception (stimulus), pain (symptom) and suffering (an integral of the two).⁸⁵ This is summarized in Figure 2.

Nociceptive pain ('opioid responsive' pain) This is caused by local tissue damage. Nociceptor subtypes exist in skin, muscle, connective tissue and viscera. There are distinctions between visceral and somatic nociceptors, although all may discharge spontaneously following sensitization. Inflammatory sources of pain may be initiated by chemical mediators affecting nociceptors. The range of neurotransmitters and modulators that have been implicated in nociception are such that the potential for various patterns of release could account for altered perception. Certainly animal models would bear this out.⁸⁶

Apart from the complexities of the nociceptors, dorsal horn and the spinal tracts, there are also descending pain-modulating pathways releasing serotonin and noradrenalin, and the ubiquitous endogenous opioids have activities at multiple sites both pre- and post-synaptically.^{87,88} Although nerve conduction itself appears not to be altered,⁸⁹ intrathecal opioids may be active at the dorsal root ganglion as well.⁹⁰

Neuropathic pain: ('non-opioid responsive' pain)⁹¹

This is pain which is unexplained by continuing tissue injury. Presumably it is sustained within somatosensory processing and represents a pathological base within the nervous system. Mechanisms include de-afferentation supersensitivity, nociceptor activation by the sympathetic nervous system or peripheral neuropathic pain precipitated

by ectopic electrical activity. It is characteristically suspected when there are dysaesthetic components to the pain. However, more than 95% of patients with neuropathic syndromes involving roots or peripheral nerves report focal pain as a presenting symptom. The absence of dysaesthesia does not exclude nerve involvement.⁹²

The relevance of distinguishing neuropathic pain is that it is less responsive to opioid drugs⁹³ and adjuvant analgesics are usually required.⁹⁴ Neuropathic pain may well respond to anti-convulsants particularly if dysaesthesia or lancinating pains are prominent.⁹⁵ Carbamazepine may be used in a start dose of 100 mg twice a day. Hanks put a ceiling of 800 mg although in our experience of HIV we have gone up to 1,200 mg without undue side effects. Valproate may also be useful in doses of 200 mg twice a day, increasing to 1,200 mg a day. Both drugs have side effects.

Membrane stabilizers such as flecainide may be helpful in neuropathic pain caused by advanced cancer, about half of cases showing a response. Side effects are unusual but may be severe. Interstitial pneumonitis⁹⁶ and cardiotoxicity^{97,98} are described, and are relevant in a differential diagnosis of breathlessness in the dying. Clonidine is reported in the management of deafferentation pain and may be given epidurally or orally in doses of 150 µg⁹⁹ increasing up to 4 mg per day. Antidepressants such as amitriptyline (start dose 25 mg), which are established in the management of neuropathic pain⁹⁵ have a long history, as do benzodiazepines such as clonazepam and are indicated if there is sleep disturbance. Drowsiness may be unacceptable. Carbamazepine, in our opinion, is the best first line drug, especially in HIV, as it is less sedative than antidepressants. Many practitioners prefer amitriptyline.

With all these drugs, we emphasize the need to explain the side effects and for the clinician to have full understanding of the pain mechanism and personality of the patient, as there may be a time delay on a therapeutic benefit, during which time both patient, family and staff may need support. Management of root or cord problems should be aggressive and requires definitive imaging such as magnetic resonance imaging¹⁰⁰ (see section on palliative:therapeutic interface).

Mixed aetiologies Neuropathic and nociceptive pain may coexist.¹⁰¹ It is poorly recognized, for example, that cancer commonly may cause nociceptive pain first, but later deafferentation type pain from nervous disruption. Cancerous deafferentation pain shares all the characteristics of deafferentation pain caused by non-malignant disease including resistance to opiates and persistence despite surgical denervation of the painful area. Treatment and strategies obviously must

Figure 2 Distinctions and interactions between nociception, pain and suffering. Reproduced with kind permission from *Lancet* 1992, 339: 1028.

differ from the conventional opiate therapy of pain caused by continual stimulation of nociceptors and continual traffic in nociceptive pathways, as the problem lies with abnormalities of function produced by deafferentation.¹⁰² Further evidence for this sequential aetiology is the beneficial effect of steroids on nerve compression. Reducing inflammatory oedema may alleviate the neuropathic element of pain and possibly therefore restore opioid sensitivity. One double-blind study confirms the benefit of steroids in this context.¹⁰³

Cancer pain syndromes do exist (Table II) and the reader is referred to Portenoy's review⁸⁴ in which he subclassifies as nociceptive, syndromes related to direct tumour involvement – acute or chronic, and neuropathic syndromes related to direct tumour involvement. There are also defined situations where pain may be iatrogenic, through surgery,¹⁰⁴ postoperative neuroma formation¹⁰⁵ and radiation fibrosis.¹⁰⁶ Radiation myelopathy is uncommon and is complicated by pain in less than 20% of cases. Imaging may be required to distinguish this from tumour involvement. Bone related disease is dealt with below.

Idiopathic pain ('total pain') This is defined when the level of pain perceived is disproportionate to the disease present and is a function of disturbance in the social, psychological or spiritual realm.⁶⁷ In support of holism at a biological level, there is some evidence for idiopathic factors influencing opiate receptors to produce pain.¹⁰⁷ Whilst it is relatively rare, its contribution to suffering cannot be overlooked. Cicely Saunders coined a phrase 'Total Pain' which is the concept attempting to integrate the aspects of suffering into the symptom of pain. Suffering may be seen as more global expression of distress or disease, of which pain may be a small or predominant part that represents integration of far more nebulous and indefinable factors.¹⁰⁸ Conceptually, therefore, analgesia may form only a component of management, although one could equally say that personal resolution is analgesic in its own right.¹⁰⁹

Opioid analgesics – some issues of relevance^{110–112}

Four main categories of opioid receptor are described, Mu, Kappa, Sigma and Delta, of which there may be subgroups, and different opiates are antagonistic or agonistic at varying sites. This is probably responsible for the differentiation of their action: for example, Mu fibres, whilst being analgesic at supraspinal level, have central effects on respiration, mood, perception and temperature regulation together with physical dependence. (Morphine type Kappa fibres are spinal and analgesic, and produce some sedation and, together with Delta receptors, may also be responsible for

respiratory depression. Sigma receptors produce dysphoria and hallucinations and are stimulatory of ventilation and the vasomotor sensor.) In theory, therefore, targeted drugs with high specificity have theoretical advantages, naloxone being a good example in that it is purely an antagonist at both Mu and Kappa sites.^{113,114}

Opioid drugs are defined as having a morphine-like action which reproduces some of the effects of the endogenous peptides – enkephalins, endorphins and 'dynorphins' – which occur naturally in the central nervous system. As stated, these may be agonists, partial agonists or antagonists acting principally in the brain stem and spinal cord.¹¹⁵ They alter the appreciation of pain, elevating the pain threshold significantly. Of 70% of patients with advanced malignancy who have pain,¹¹⁶ the majority will require an opiate at some stage. Between 30 and 40% of patients in hospital receive opioids of one kind or another. Opioids are very widespread in their use within anaesthesia and acute analgesia apart from their use in palliative medicine.¹¹⁷ Eighty per cent of patients with cancer pain will be controlled with oral medication.⁷⁷

'Opioid responsiveness' Practically, the terms opioid responsive and opioid non-responsive pain are helpful but not absolute and arise from observation.^{118,119} A working definition of opiate non-responsiveness is pain that is inadequately relieved by opioid analgesics given in a dose that causes intolerable side effects despite routine measures to control them. Certainly there is evidence that opioids in sufficient dose do have some effect on neuropathic pain.¹²⁰ Hence, as Hanks remarks in one review,⁸² most cancer patients have multiple origins for pain and opiates will be useful to some extent in all of them. The need to record and quantify these elements is important and should be done with the patient using a pain chart to establish baseline and to track the response to treatment.¹²¹

The concept of the analgesic ladder is now well established.⁷⁷ Non-opiates such as paracetamol or non-steroidal anti-inflammatory drugs play an important role either in their own right or as adjuvants. There should not be undue concern about the use of paracetamol in doses up to 5 g per day. In patients with multi-system disease such as HIV-related problems, other drugs' metabolism may be influenced by paracetamol, most specifically zidovudine, and account should be taken of this in prescribing.

Weak opioids Despite the arguments against using co-proxamol, it remains the basic weak opioid combination used by most practitioners in doses up to 12 tablets daily. The combination of a non-opioid and weak opioid is logical for pain at this level.

Table II Cancer pain syndromes. (Reproduced with kind permission from *Lancet* 1992, **339**, 1029)

Table IIa Common pain syndromes associated with chronic pain in cancer patients

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1. Chronic nociceptive syndromes
Related to direct tumour involvement
(a) Neoplastic damage to bone and joints
 Base of skull
 Orbital syndrome
 Parasellar syndrome
 Sphenoid sinus syndrome
 Middle cranial fossa syndrome
 Clivus syndrome
 Jugular foramen syndrome
 Occipital condyle syndrome
 Vertebral body
 Atlanto-axial syndrome
 C7-T1 syndrome
 T12-L1 syndrome
 Sacral syndrome
 Long bones
 Generalized bone pain
 Multiple metastases
 Diffuse infiltration of bone marrow
 Direct infiltration of a joint
(b) Neoplastic damage to viscera
 Shoulder pain from diaphragmatic infiltration
 Epigastric pain from pancreas cancer (or other upper abdominal neoplasm)
 Right upper quadrant pain from distension of hepatic capsule
 Diffuse abdominal pain from peritoneal disease or chronic intestinal obstruction
 Suprapubic pain from infiltration of bladder
 Perineal pain from infiltration of rectum or perirectal tissues
(c) Neoplastic damage to soft tissues
 Infiltration of skin and subcutaneous tissue
 Infiltration of muscle and fascia in limbs
 Infiltration of muscle and fascia in neck or head
 Chronic damage to oral mucous membranes

Related to therapy
(a) Postoperative pain syndrome related to non-healing incision
(b) Post-radiotherapy pain syndromes
 Prolonged enteritis
 Damage to skin and subcutaneous tissues
(c) Post-chemotherapy pain syndromes
 Aseptic necrosis of bone
 Steroid pseudorheumatism

2. Chronic neuropathic pain syndromes
Related to direct tumour involvement
 Peripheral nerve syndromes
 Paraspinal mass
 Chest wall mass
 Retroperitoneal mass
 Painful polyneuropathy (as a remote effect of the neoplasm)
 Brachial, lumbar, sacral plexopathies
 Leptomeningeal metastases
 Epidural spinal cord compression

Related to therapy
(a) Postoperative pain syndromes
 Post-mastectomy

- Post-thoractomy
Post-radical neck dissection
Post-nephrectomy
Post-amputation
(b) Post-radiation pain syndromes
 Radiation fibrosis of brachial or lumbosacral plexus
 Radiation myelopathy
 Radiation-induced peripheral nerve tumours
(c) Post-chemotherapy pain syndromes
 Chronic painful polyneuropathy
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Other chronic pain syndromes include myofascial pains and headache.

Table IIb Common acute cancer pain syndromes

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1. Acute nociceptive syndromes
Related to direct tumour involvement
(a) Neoplastic damage to bone and joints
 Pathological fracture of long bone or vertebra
 Incident pain related to movement of damaged bone (from bone itself, connective tissue, or muscle spasm)
(b) Neoplastic damage to viscera
 Acute intestinal obstruction
 Obstruction of biliary tract
 Obstruction of ureter
 Acute stretch, compression, or torsion of organ capsules or related connective tissue

Related to therapy
(a) Acute postoperative (incisional) pain
(b) Post-radiotherapy syndromes
 Incident pain associated with positioning
 Oral mucositis
 Enteritis or proctitis
(c) Post-chemotherapy syndromes
 Acute meningial syndrome associated with intrathecal methotrexate
 Oral mucositis
 Myalgias and cramps
 Associated with tumour embolization
 Extravasation with soft-tissue injury
 Chemical pleurodesis
 Multiple intramuscular injections

Related to diagnostic procedures
 Incident pain associated with positioning
 Venipuncture
 Bone marrow aspiration and biopsy

2. Acute neuropathic pain syndromes
Related to direct tumour involvement
(a) Brief exacerbations of chronic neuropathic pains (paroxysmal lancinating or short-lived pains)
(b) Acute radioculopathy associated with vertebral collapse

Related to therapy
(a) Postoperative pain related to acute nerve injury
(b) Lhermitte's sign following spinal cord irradiation
(c) Post-chemotherapy painful polyneuropathy
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Other acute pain syndromes include: headache (related to tumour, related to therapy and other); acute abdominal pain associated with constipation (related to tumour related to therapy, and other); and acute herpes zoster.

Strong opioids Morphine is the drug of choice by mouth and, for the purist, the dose requirement should be titrated with immediate release formulations, such as the elixir or tablets given 4 hourly, where peak plasma concentrations are achieved within the first hour. Partial agonists such as buprenorphine should be avoided. One of the unique aspects of pain control with morphine is the dose range of the order of the 1,000 fold (2.5 mg 4 hourly to 2.5 g four hourly or more). However, the majority of patients require less than 200 mg per day. Because of this enormous therapeutic range, dose titration is best done on a 4 hourly dosing, with top ups during that period for breakthrough pain of the same dose, although some practitioners would prefer to use a 50% dose top up with a 50% increase in the next scheduled dose. This usually ensures adequate pain control within 24–48 hours. It is essential in assessing response to the pain to take account of other factors such as severity, nature and affective component. Maintenance analgesia is best prescribed in a slow release preparation which only requires twice daily dosage, although immediate release should be available for breakthrough pain.¹²²

Relevant side effects¹¹² Respiratory and cough depression, reduced intestinal motility, nausea, vomiting and retention are common to all opiates as is tachyphylaxis. Hypersensitivity has been reported. The various analogues express the side effects as well as the effects on pain control in varying degrees. Sedation usually resolves within a few days and hallucinations/confusion are unusual. Where a patient has hallucinations, it is likely to be a function of some internal conflict and should be explored in that light.

The gut All opioids stimulate the chemoreceptor trigger zone. This is dose related. Antiemetics are effective, especially those active on dopamine receptors.¹²³ There is an additional potent effect on vestibular apparatus,¹²⁴ reduction in propulsive peristalsis and an increase in contractility and sphincter tone in the gastric antrum which delays emptying.¹²⁵ Naloxone antagonizes the delay although it is partially active in this respect.¹²⁶ Apart from hypomotility, constipation is aggravated by a reduction in intestinal secretion. Gastric, biliary and pancreatic secretions are also reduced. Clonidine has been reported to have beneficial effects in reversing these effects.^{127,128} Nausea and vomiting is likely to occur in a half to two third of patients, and most practitioners would recommend an antiemetic to begin with the morphine, although opinions differ on this. Hanks recommends haloperidol 1.5 mg nocte or twice daily.

Mechanisms of opioid respiratory depression These are dose related and closely linked to analgesic effect. Respiratory depression is confirmed by physiological measurements of reduced CO₂ responsiveness.¹²⁹ A direct action on pontine and bulbar respiratory receptors makes patients dependent upon hypoxic drive,¹³⁰ although extradural injection of opiates is also associated with respiratory depression but there is a time delay of some hours (presumably dependent upon cerebrospinal fluid circulation reaching the respiratory centre). The incidence is extremely low.¹³¹ Respiratory depression may be antagonized by physostigmine as well as by opioid antagonists with preservation of the analgesic action.¹³²

Interestingly, the presence of pain is effective in overcoming the respiratory depressant effects, hence abolition of pain by, for example, neural block in patients treated with opioids has been followed by respiratory depression because of persisting unopposed opioid action.¹³³ This has led Hanks and Twycross to the hypothesis that pain is a 'physiological antagonist' of opioid activity.¹³⁴ The association of opioids with acute retention is probably due to action at cord level within the thoracic spine as some sympathetic neurones contain enkephalins and substance P.¹³⁵

Anxieties about addiction is no bar to opioid use in pain control. Whilst tolerance and dependence is well known, the Boston Collaborative Drugs Surveillance Program documented only four of 11,882 patients receiving opiate analgesics as being dependent. This group had no previous history of addiction.¹³⁶ Tolerance appears to develop in all patients receiving opioids on a chronic basis. Problems with withdrawing can be avoided by gradual decrease in daily doses; the incidence of addiction in cancer patients taking opioids chronically is probably no greater than 0.1%.¹³⁷ With respect to chronic, non-cancer pain, opioids may be the only effective treatment and dependency seems to be a minor problem with appropriate management.^{138,139} The St Christopher's study on motor neurone disease, for example, showed no problems with opioids, one patient taking morphine for over 5 years in a stable dose. Furthermore, within this group there was a low incidence of depression (7%).⁷⁵

Prescribing

Routes of administration It is possible to deliver drugs very effectively by mouth. This is the route of choice even when strong analgesia may be required. Twice daily treatment with controlled-release preparations is most effective, balancing the need to achieve effective drug levels with patient compliance. There is also evidence to suggest that both

pain levels and total morphine dose are lower using slow-release morphine.¹⁴⁰ Slow-release morphine preparations are now coming on to the market in liquid form.

There is no evidence that the use of parenteral opiate is advantageous by virtue of pharmacokinetics, perhaps with the exception of spinal routes in selected cases. The decision to use a syringe driver or intravenous infusion depends upon factors such as gut function, nausea and vomiting, or conscious level.

Diamorphine is highly soluble and is the drug of choice for parenteral use. The conversion dose from oral to parenteral morphine is the subject of some discussion and is summarized by Hanks.¹⁴¹ The generally accepted conversion is 3:1. At the end of the day, the index is pain relief and, as most patients in converting need an increase in dose, we use a factor of 2.5. There may be a place for intravenous infusions if subcutaneous administration is not tolerated or precise control is needed where, say, pain is fluctuating in intensity.¹⁴² Because of the simplicity, technical advantages, and cost-effectiveness of continuous subcutaneous opioid infusion into the arm, chest wall or trunk, routine intravenous opioid infusion for the management of severe cancer pain should be abandoned. The use of portable 24 hour syringe drivers is now widespread and long-lasting machines will now infuse drug for up to 37 days.¹⁴³

Transdermal opiates such as fentanyl have also been used, but therapeutic blood levels took some time to achieve and the drug was slow to be cleared from the circulation on stopping the therapy. In the same study, inhaled opiates were used and were found to have an acceptable analgesic effect with few side effects.¹⁴⁴

There is a case for using spinal opioids in patients with intolerable side effects from systemic morphine, as the doses required are significantly smaller. Opinions vary on the appropriateness of this technique which is probably most effective for lower body pain, and careful review should precede any decision to engage in long-term therapy.^{145,146} Opiate may be mixed with local anaesthetic. However, as the number of patients requiring this form of administration is small (16 out of 1,205 in Hogan's study¹⁴⁷), controlled trials will be difficult to conduct. In the meantime there are anecdotal reports of the use of other medication such as clonidine, somatostatin, midazolam, calcitonin and ketamine.⁸⁴

All analgesic drugs should be given on a regular basis. If patients are allowed to wait until they suffer pain before it is relieved, they are likely to need higher doses of analgesics than if the pain is constantly and consistently treated before breakthrough. Should a given dose be inadequate, the dose should be increased rather than the drug

interval shortened.

Acute or breakthrough pain on the background of controlled chronic pain is poorly understood but is sufficiently common to merit the availability of opiate for its management.¹⁴⁸

Adjuvant therapies

Drugs Because of the complexity of pain, adjuvants may themselves not need to be analgesic if they are dealing with other aspects of suffering, hence the use of diazepam, midazolam and methotrimeprazine. Views vary on the best medications for the preterminal phase of care where there may be restlessness.¹⁴⁹ Non-steroidals and steroids have established value as adjuvants, and therapeutic interventions have a place (see below).

Topical treatment Use of benzydamine (Diffiam) is known to be effective in the oral ulceration and pain following radiotherapy and chemotherapy.¹⁵⁰ This is a unique non-steroidal with local anaesthetic properties and is absorbed transdermally. Three per cent aqueous-based cream of benzydamine used on pressure sores shows impressive results with complete pain relief in 29 of 30 ulcers at 24 hours.¹⁵¹ For neuropathic pain, topical capsaicin may have a place, although the data are sparse at present.¹⁵²

Nerve blocks¹⁵³ There are many nerve-blocking techniques available which may be used to add to the quality of life of the terminally ill either as a supplement to other therapies or to reduce the side effects produced by drug and adjunctive therapies.¹⁵⁴ For coeliac plexus block, review of 136 patients confirmed that 75% had good and permanent pain relief and that radiological control of needle placement affected neither quality of pain relief nor the complication rate. Coeliac plexus block for pancreatic pain has recently come under critical review.¹⁵⁵

The problem with nerve blocks is not only their lack of permanence, but also the potential for side effects which sometimes may make them more troublesome than they are worth. Specific pains originating from, say, the pancreas or from rib problems respond well to coeliac block or intercostal blocks. However, to see nerve interruption as a solution to localized pain is probably naive: a good illustration of this being pleural involvement due to mesothelioma or lung cancer, where intercostal block will be inadequate probably because pain is transmitted through the sympathetic fibres.⁹¹

Using a cost-benefit ratio there is a high incidence of complications using nerve blocks particularly if patients develop motor weakness or

incontinence. This may well be unacceptable given that combined oral analgesia and careful management is likely to make a significant impact on pain.

Surgery There is a place for percutaneous anterolateral cordotomies which may be effective for some months. Again these should be considered with care, although they have a place with pelvic disease and with mesothelioma.¹⁵⁶ A comprehensive discussion of the various neurosurgical options is found in Tasker's paper. Likewise, orthopaedic surgery has a place in appropriate circumstances with problems relating to cord compression stabilizing the spine, or with pathological fractures.¹⁵⁷

Psychological strategies In talking about psychological coping strategies, Davidson⁸³ says two things. He comments about hospitals exhibiting a kind of institutional denial of pain and dying, with the perceived penalties being that family visit less often, or staff label the person as difficult, or detach themselves by putting psychological distance between themselves and the problem. He maintains that psychologically a problem is solved either by changing the perception of events or by changing the environment itself. In a clinical model this would be medication such as opioids or targeted treatment such as local radiotherapy, whereas psychologically, action-centred methods such as assertiveness training may provide an 'external' coping strategy. Patients, however, may use 'internal' mechanisms such as avoidance and denial as to what is really happening on the one hand, or information searching by obsessional reading on the other. Finally, hopelessness and inertia are particularly negative forms of coping. Such strategies may be helpful in the short term, however, in the long-term dying patients need to be helped to let go gradually.

One writer with cancer, speaks of using positive activities to wonder whether 'the positive emotions produce positive chemical changes? Is it possible that love, hope, faith, laughter, confidence and the will to live have therapeutic value? Certainly his view that positive mental attitude may influence cancer survival is held by many and refuted by others.¹⁵⁸

The way Davidson suggests for coping with these is to involve patients as active members of the team. (From our point of view this is the paradigm of management of HIV disease.) There is no doubt that psychiatric services are helpful in some cases.^{159,160} Psychotherapy would look at the significance and symbolism of symptoms or life events in an attempt to help the patient see meaning within his or her illness.¹⁶¹ For example, the symbolism of dependency, guilt and suffering, or the function of the pain within the family system

may be examined usefully. Low self-esteem is certainly linked with low pain thresholds¹⁶² and there is a place for support groups to empower people,¹⁶³ and complementary therapies such as biofeedback,¹⁶⁴ acupuncture and art therapy¹⁶⁵ may merit consideration.

Breathlessness¹⁶⁶

Incidence

Dyspnoea, a threatening common symptom with tumours is reported to occur in 29–74% of patients with terminal cancer at some point in their illness.¹⁶⁷ In a study by Heyse-Moore of 303 patients admitted to hospice, 55.5% overall were dyspnoeic on admission. In those surviving for less than a day after admission, however, the prevalence was 78.6%, with 11.4% rated as severe. Survival was significantly shorter as severity of dyspnoea increased. Dyspnoea was more likely to be present in those with carcinoma of the bronchus and breast, and those with lung metastases.¹⁶⁸ In HIV, breathlessness and cough are commonly encountered symptoms in terminally ill patients, are particularly difficult to control and are the main clinical determinant of in-patient death.¹⁶⁹

Management

Opiates are probably the most effective treatment for dyspnoea and may be administered orally, intravenously, subcutaneously or via a nebulizer. One study of morphine on the dyspnoea of terminal cancer patients looked at 20 patients with dyspnoea using subcutaneous doses of 5 mg morphine or 2.5 mg regular dose of morphine if they were already taking it for analgesia. Nineteen out of 20 patients reported improvement in their dyspnoea following the morphine without significant changes in respiratory rate, respiratory effort or arterial blood gas value.¹⁷⁰ The beneficial effect of morphine on the perception of breathlessness is supported in other studies in lung cancer using intravenous morphine.^{171,172} The usual starting dose was 5 mg 4 hourly with a double dose as needed at night. Mechanisms postulated by Cohen for the improvement were the action of morphine on medullary chemoreceptors to decrease the patient's tidal volume and response to hypercapnia.¹⁷² This should decrease respiratory drive and relieve dyspnoea. Morphine would also act to decrease the patient's anxiety, cardiac pre-load and pain. There is some evidence that nebulized opiates may have a favourable effect on the sensation of breathlessness.¹⁷³

Corticosteroids have been known to improve sensation of terminal dyspnoea. The anti-inflammatory effects of steroids seem to reduce

oedema and inflammation around tumour and may be used to treat airway obstruction, lymphangitic pulmonary metastasis and superior vena caval obstruction. Studies using benzodiazepines for dyspnoea have shown conflicting results,^{173,174} but there have been encouraging reports of the use of nebulized local anaesthetic as possible palliative therapy for dyspnoea. The suggested mechanism is anaesthesia of J receptors in the large airways,¹⁷⁵ by Santolicandro *et al.*¹⁷⁵ who reported a study involving four patients with emphysema with frequent complaints of dyspnoea at rest. Inhaled nebulized lidocaine was used once a week and, 3–5 hours after inhalation, all patients reported they could breathe more easily and more deeply with a reduction of dyspnoea. The subjective improvement was reported to last 2–3 days. Winning *et al.*¹⁷⁶ report inconclusive findings from studies, although there is anecdotal evidence suggesting that the technique of nebulized local anaesthetic may be useful in dyspnoea in some patients. DeConno reported favourably on the use of local anaesthetic in the treatment of breathlessness and cough.^{177,178}

Anticholinergics may be used to relieve respiratory secretions contributing to shortness of breath and to abolish the noisy breath or 'death rattle' caused by accumulating secretions, mainly in the upper airway, in weak, moribund patients. Hyoscine in particular is used for this and may be administered subcutaneously, as a continuous infusion.¹⁷⁹

Constipation

Management of the gut¹⁸⁰ is an important aspect of palliative care.

Once again, we find aspects of meaning hidden in the language of this symptom; *katharsis* (Greek) meaning 'cleansing' and *purgativus* (Latin) meaning 'purifying'. It is not surprising, then, that disordered bowels may cause people distress over and above their biological effect, and a national preoccupation with regularity – 10% of our population consider themselves constipated – has found its way into humour.

Constipation is an occupational hazard in opioid therapy, in the care of the immobile, chronically sick and dying. If left unmanaged, it is uncomfortable and debilitating. In the dying it may be the sole underlying cause of abdominal pain, urinary retention, restlessness and confusion or subacute obstruction. Poor food and fluid intake merely compound matters. In most cases, bulking agents are not appropriate due to the quantities for an effect. Osmotic agents (for example, lactulose), surface-wetting agents (for example, ducosate) and stimulants such as bisacodyl (a polyphenolic), senna or danthron (both anthracenes) are all used alone or in combination. In a recent review of

laxative use in hospice, drug charts of 100 inpatients with terminal cancer were reviewed. Sixty-two per cent of patients received an oral laxative regularly, 60% received co-danthrusate (combined danthron and ducosate) or co-danthramer (combined danthron and poloxamer 188). A total of 23% received senna and 21% lactulose; eight patients received two laxative preparations concurrently; 37 patients needed rectal measures. About half of those not taking a strong opioid required a regular laxative compared with two-thirds of those on a strong opioid. There was no correlation between the dose of morphine and that of co-danthrasate.¹⁸¹ Provided combinations of osmotics/wetting agents and stimulants are logical, patients' perceptions of benefit are evenly distributed between the two sorts of drugs.¹⁸²

Recently, with respect to opioid-related constipation, a more erudite approach has been to use a specific antagonist. The low bioavailability of naloxone and postulated local effects of opiates on the gut led to studies of oral naloxone.¹⁸³ In a placebo-controlled study, naloxone was laxative, with a dose response. The authors conclude that results were encouraging, that there was no adverse effect on pain control, and that there was a possible useful effect on constipation.¹⁸⁴

Use of anticholinergics in diarrhoea and constipation

Anticholinergics (hyoscine hydrobromide and hyoscine *n*-butyl bromide – buscopan) are used widely in palliative care to relieve the colic and pain of gastrointestinal obstruction including the pain from pancreatic and biliary trees.

Intestinal obstruction due to malignancy can be treated very successfully without nasogastric suction or intravenous fluids. The basis of this is to create a pharmacological ileus and to enhance fluid absorption from the proximal bowel. Together with opiate, hyoscine forms the basis of the medical management of intestinal obstruction,¹⁸⁵ although hyoscine may be sufficient alone.^{186,187}

Buscopan (hyoscine butylbromide) can be useful in the resistant diarrhoea that is common in late stage HIV disease.¹⁸⁸ Combination therapy with diamorphine in a syringe driver has been successful in controlling symptoms and allowing weaning on to oral preparations, or continued subcutaneously for more than 3 months in particularly resistant cases.

Octreotide is a native inhibitor of somatostatin. With respect to gut pathology, it inhibits endocrine and exocrine gastrointestinal secretion, reducing both mobility and secretion of gastrointestinal hormones.¹⁸⁹ Early studies in refractory HIV-related diarrhoea are encouraging.¹⁹⁰ It may also be

useful in the reduction of fluid secretion from pancreatic fistulae.¹⁹¹

Nausea and vomiting^{183,192}

Forty-two per cent of terminally ill patients have nausea and 32% vomiting. These symptoms are almost as distressing as pain.¹⁹³ Nausea and vomiting are commonly encountered symptoms, with a variety of causes, the commonest being the primary disease process, or side effects of 'curative' treatments such as chemotherapy or analgesics. Like breathlessness, nausea and vomiting are a crude common pathway for a variety of stimuli. However, there are some clinical indices of use: gastric stasis or outflow obstruction gives large volume, effortless vomiting with hiccoughs, reflux, and brief, episodic nausea. The main pharmacological culprits are opioids.

Squashed stomach syndrome, due to external, generalized compression without outflow obstruction, is familiar to palliative physicians, where food tolerance is poor, nausea frequently persistent and food related.¹⁹⁴ Do not be caught out by constipation and always consider hypercalcaemia as a cause of vomiting.

Regnard and Comiskey summarize the mechanisms of nausea and vomiting, and provide very helpful algorithms of investigation and treatment.¹⁹⁵ They favour cyclizine (an antihistamine) or hyoscine hydrobromide as first line for symptoms likely to be triggered by vagal or central action on the vomiting centre. For the chemoreceptor trigger zone, dopamine antagonists are logical to use. The long half-life of haloperidol (16 hours) often allows a single nocturnal dose to be effective.^{195,196}

Metoclopramide or domperidone, both substituted benzamines, apart from being potent central dopamine antagonists, act peripherally to increase gastric emptying. Whilst domperidone has a narrow therapeutic range, it does not cross the blood-brain barrier and avoids extrapyramidal side effects.^{183,197} The related drug cisapride has a broader 'normalizing' effect on gut motility,¹⁹⁸ but is expensive. Empirically, very high dose steroid, reducing rapidly over 10–14 days, may be effective in squashed stomach or obstruction. It may be worth considering active interventions such as radiotherapy or laser endoscopy (see below).

Antiemetics may be given orally, intramuscularly, intravenously or by continuous subcutaneous infusion. Rectal, sublingual and transdermal preparations are also available. In a study by Francis *et al.*, the use of transdermal scopolamine patches is described to manage opiate-induced nausea and vomiting. Blood levels of scopolamine given via patch were said to take 12 hours to build to equilibrium and then to take 12 hours to dissipate

upon patch removal. Nausea improved rapidly in an average of 1.3 days in 11 out of the 13 patients and the only medication change was the patch in nine of these patients. Venting percutaneous gastrostomy may be useful in the management of patients with nausea and vomiting or visceral pain due to terminal advanced intra-abdominal carcinomatosis.¹³

For patients requiring a syringe driver, diamorphine is compatible with haloperidol, hyoscine hydrobromide, and metoclopramide.^{199,200} Cyclizine, however, is poorly soluble and crystallizes above 20 mg/ml.²⁰¹

Corticosteroids

Steroids are a panacea of considerable use in palliation where the beneficial effects on mood, appetite, well-being and nausea and vomiting are very helpful. There are also specific indications such as reduction of oedema, either as part of pain control or in the control of cerebral oedema. Whilst there are theoretical objections to their use in HIV disease due to their effect on immunity, their effect on the oedema associated with Kaposi's sarcoma, whilst short term (a median effectiveness of 12 weeks), is clear and judicious use undoubtedly improves quality of life.^{202,203}

The benefit of steroids in emesis was first reported in chemotherapy-induced vomiting,^{204,205} the theoretical base being their antiprostaglandin effect. Studies have now established their place alongside other major antiemetics.^{206,207}

The only substantial evidence suggesting that steroids increase the likelihood of peptic ulceration is when they are given concurrently with non-steroidals.²⁰⁸ The reviewers say there is little point in giving H₂ blockers with steroids routinely,²⁰⁹ but a subsequent letter proposed that in the management of ulceration due to either drug, misoprostol is the drug of choice as a prostaglandin E₁ analogue which reverses the effects both of steroids and indomethacin.²¹⁰

The therapeutic palliative interface

Aids – the therapeutic dilemma^{211,212}

AIDS brings some different problems for the palliative physician. Quite aside from the inevitable challenges of unfamiliar symptoms such as uncontrolled diarrhoea,¹⁹¹ or unusual tumours such as Kaposi's sarcoma, the syndrome, whilst universally fatal, comprises infective elements that are treatable and potentially at least, curable. Furthermore, the management of many complications requires long-term maintenance programmes or prophylaxis for opportunistic infections such as

cytomegalovirus (for example, retinitis), herpes simplex (oral and genital), cerebral toxoplasmosis, cryptococcal meningitis and a variety of other infections. Furthermore, drug regimes are changing, many are parenteral and most require biochemical or haematological surveillance.

The challenges for good palliative practice are obvious and the sense and logic for using a philosophy of cost-benefit is self evident on therapeutic grounds alone. This is compounded by the grey area between palliation and cure. As with death in the young from other causes, the aggressive and curative avenues are trodden far later in the natural history of disease. Patients may be coping by denial, and resisting the truth; family dynamics are often convoluted and divided between biological and social family. However, clinical uncertainty is such that there is often a very real possibility of buying good quality time for someone who may appear moribund, either with aggressive interventions or judicious palliative measures where there is a potential quality-time tradeoff.

It is for these reasons that there is a need for very close liaison with acute physicians and an active inclusion of the patient and 'family' at all stages of the therapeutic and decision-making process. On the positive side, patients are young and well informed, and find it easy to understand and cooperate in treatment decisions, achieving goals, etc. Applying the philosophy in specific case studies is in the literature.^{47,48} The hospice movement is already engaging the challenges of HIV, where it is essential to decide where services stand with respect to acute intravenous therapies and to have quick and confidential access to the local AIDS designated physician and acute beds.¹⁸

It must be said that if we as a movement are actively to engage the care of the young dying with any disease, the management of HIV is a demanding and rewarding training ground.

Bone disease

Pain

Bony metastases are the commonest cause of cancer pain.²¹³ They occur in 85% of patients with carcinoma of the breast, 85% prostrate and 60% lung. Management is almost exclusively palliative with cure being very rare. The place of radiotherapy, chemotherapy and, in certain circumstances, surgery, according to the tumour type, may be appropriate.²¹⁴ Surgical intervention is not established practice. Endocrine treatments are first line in prostrate and breast cancer with median effectiveness of 12-20 months.²¹⁵ In 20-50% pain relief may be dramatic.²¹⁶ Systemic treatment

for prostrate cancer is 60-90% effective.²¹⁷ External beam radiotherapy is the best treatment for localized disease. Single dose is as effective as fractionated, and is more appropriate for palliation. Radiotherapy may take 2 weeks to be effective. Symptomatic success is of the order of 85%.²¹⁸

Inhibition of osteoclastic activity is a logical approach to the reduction of bone turnover that may result from tumour-related cytokines released locally. Calcitonin, mithramycin and gallium have been examined in this respect. Biphosphonates - analogues of naturally occurring pyrophosphate - probably inhibit osteoclastic activity.²¹⁹ Diphosphonates are established treatments in Paget's disease and malignant hypercalcaemia. However, there are no conclusive placebo trials showing benefits on pain, although small study results are encouraging. The main problem is getting large enough samples and methodology that minimizes placebo and observer error. Pain relief and biochemical improvement is seen in hormone-resistant prostate cancer.²²⁰ Bone-seeking isotopes may be effective in prostatic carcinoma.²²¹ Comparative studies suggest that pamidronate is the most effective at controlling symptoms as clodronate and etidronate have unacceptable side effects.²²²

Surgical stabilization of long bones with extensive subcortical destruction may be done 'prophylactically',²²³ and there are arguments for aggressive prosthetic surgery for pain relief and maintenance of skeletal integrity.²²⁴

*Hypercalcaemia*²²⁵

The incidence of hypercalcaemia in malignancy in a series of 200 was 8.5%, although six of 43 with carcinoma of the bronchus were hypercalcaemic (14%).²²⁶ The consensus now is that corticosteroids do not influence malignant hypercalcaemia significantly.²²⁷ Consequently, aggressive parenteral treatment is well established in hypercalcaemia and may merit admission to hospital if palliative services do not routinely give intravenous treatments.

Clinical signs may be few. In one recent study, only five out of 17 hypercalcaemic patients had known bone secondaries.²²⁸ Amongst 200 other cases reviewed, 13 had no nausea or vomiting. Only three had severe symptoms, two of whom also complained of severe thirst. The most noticeable symptom was moderate or severe drowsiness (53%). Hypercalcaemia should therefore be suspected in unexplained drowsiness in cases of carcinoma of the bronchus, breast or female genital tract. Biphosphonates are now considered first-line therapy.²²⁹

Invasive procedures

Invasive procedures such as endoscopy mean that day case or 48 hour admissions to acute units may be necessary. In terms of time expenditure, this is little different from some radiotherapy or other accepted procedures such as symptomatic blood transfusion. However, a therapeutic ratio must be applied, and the fact that a lesion may be treatable does not necessarily mean that treatment will be beneficial.

Gut endoscopy²³⁰

Oesophagus strictures respond well to endoscopic treatment. Simple dilatation can be done with light sedation under direct vision with or without the insertion of a celestian tube.²³¹ Dilatation is a repeatable procedure done as a day case and lasts 10–15 minutes with light sedation. Perforation is a recognized complication, particularly with malignant strictures. Bleeding is relatively common but seldom requires transfusion, when prosthetic tube or laser therapy may be the procedure of choice.^{232,233} Beneficially symptomatic relief is immediate. In malignant stricture, the case for laser is good and the procedure should be judged case by case.²³³

Previous radiotherapy does not preclude dilatation but perforation may be more common. Biliary stents can also be inserted endoscopically and may be very helpful in symptomatic obstructive jaundice.^{234–236} Endoscopic stenting is successful in up to 96% of cases.²³⁷ Eighty per cent have reduction in jaundice and/or stop itching. The survival of the stents is between 6 and 36 weeks with replacement being a relatively straightforward procedure.

Percutaneous endoscopic gastrostomy – this can be done without general anaesthetic – is relatively simple and, once in place, is comfortable with reduced risks of inhalation and inflammatory problem within the oesophagus. It is not, however, generally accepted in this country as a useful procedure.

Rectal laser therapy which does not require anaesthesia may be useful for the palliation of mucus discharge, bleeding and tenesmus due to tumour bulk, and may provide an option for relief of obstruction unless medical management is indicated for general reasons.

Bronchoscopy²³⁸

Five years survival with bronchial carcinoma remains poor at 8% largely because of late presentation. The particular benefit of laser is in the relief of obstruction especially of tracheal tumours. The technique is described in a paper reviewing the

author's own work. About 75% of patients had symptomatic improvement with 63% having objective improvement in peak flow exceeding 25%, with partial obstruction of a major airway. Within the study of 100 patients, 24 had haemoptysis with 58% having complete abolition for one month and 67% significant relief. Sixty-eight per cent of the total group had a symptomatic response and 56 or so had an objective response to treatment. There were two operative deaths with haemorrhage and asphyxia under local anaesthetic although general anaesthetic is now considered much safer.²³⁸

Laser may also be particularly helpful in emergency presentation of acute respiratory distress from tracheal tumours.²³⁹ Having established a safe airway there can be subsequent treatment to maintain in the relief of stridor. The median survival of the group described by George *et al.*²³⁹ was 180 days.

The terminal phase

Nutrition and fluids are a source of anxiety and debate in terminal care. However, there is little evidence that anorexia, starvation or dehydration are unpleasant at this stage.¹⁹⁷ Interestingly, in a study of 14 patients, 71% indicated that they would prefer family members to be less assertive and simply let them choose what and how much they wanted to eat. Family members may cope better with the anorexia if they have knowledge that it is physiologically explainable and an accepted consequence of the disease over which the patient has little control. Until the discovery of an effective means of arresting, controlling or reversing the anorexia of cancer, professional efforts will be most effective if they are focused on helping patients and families identify and address the feelings that accompany the significant loss. As family members gain comfort with the patient's inability to eat, so they move towards acceptance of the impending death.²⁴⁰

However, with debility and dehydration in the terminal stages of illness, oral discomfort is common. Causes may be specific, when targeted treatment may be appropriate, though antibacterial mouthwashes such as chlorhexidine used three times a day or local anaesthetic agents in spray form such as benzydamine may be helpful for any sort of oral pain and can be used on an as required basis. Anular stomatitis may respond to clobetasone, nystatin, oxytetracycline (Trimovate) cream.

Dehydration and poor oral intake may exacerbate mouth pain, causing dryness and a greater tendency for skin and mucosa to crack, as may the use of anticholinergics. Simple measures such as

oral sponges on sticks for moistening, sucking ice cubes and frequent saline or water mouth washes may work. Artificial saliva such as Glandosane spray is another possible useful adjunct.

Medication

The use of syringe drivers to deliver continuous subcutaneous drugs has revolutionized unobtrusive medication in the terminally ill. Diamorphine, antiemetics and anticholinergics can be mixed in the same syringe to give optimum control of symptoms in any environment.²⁰³

In patients with restlessness or preterminal distress which is uncharacterizable (so-called terminal restlessness), midazolam has proved very effective in median doses of 30 mg.^{151,241,242} Methotrimeprazine, a non-irritant phenothiazine with analgesic properties may also be effective as it is approximately twice as sedative as chlorpromazine.

Conclusions

A word about euthanasia^{243,244}

Euthanasia is not a moral, social or clinical solution to the difficult questions and conflicts of human suffering. Even in the very small minority of patients where pain control is a very difficult problem, there is never a situation where nothing can be done by anyone. The question is how to access the multidisciplinary resource.

To address this issue, we must move away from ordinary and extraordinary, as all interventions are

weighed in terms of their benefit and plausibility related to the patient's best interest. This dispenses with the notion of the prolongation of life being secondary. However, to play with words and call this passive euthanasia (Rachels argues for, and defines 'Passive euthanasia' as '... simply refraining from doing anything to keep the patient alive'²⁴⁴) is at best illogical or simplistic and at worst strategic. Irrationality such as this leads to practitioners being unaware of or unable to seek assistance, blocks the delivery of palliative care, and makes well-intentioned clinicians vulnerable to the pressures of helplessness and malpractice. Many think that the acknowledgment of the reality and truth of death may in some be 'prophetic' and cause a patient to give up. This is compounded by folklore and myths about opiates as addictive vehicles of the Angel of Death and only for the end, and by the prejudice amongst those wedded to the therapeutic model that palliation is in some way the poor relative and refuge of the destitute.

Collusion with the notion that treatment at all costs is good medicine, or that hope and treatment are the same thing, is common between families and practitioners, and may be due in part to modern culture's unfamiliarity with death and its process. 'To withhold an ineffective treatment because it would have little chance of working (if the cost is too great) is simply avoiding the futile.'²⁴⁵ This is very different from the intentional decision to kill. Whilst balancing the need for (absolute) symptom relief with the risk of death, in the terminal phase, death as a relief may be a truth, but to see it as a therapeutic modality or means of achieving relief is not palliative medicine, but euthanasia.

References

Background

1. Saunders, C.M. *The Management of Terminal Disease*. Edward Arnold, London, 1978.
2. Tuohy, J.F. *Caring for Persons with AIDS and Cancer*. Catholic Health Association of the United States, St Louis, Missouri, 1988.
3. *The Oxford English Dictionary*. Oxford University Press, Oxford, 1963.
4. Holford, J.M. *Terminal Care, Care of the Dying. Proceedings of a National Symposium held on 29 November 1972*. London, HMSO, 1973.
5. European Society for Palliative Care. Newsletter No. 1. 1989.
6. Dunstan, G.R. Clarifying the issues. In: Twycross, R.G. & Ventafridda, V. (eds). *The Continuing Care of Terminally Ill Cancer Patients*. London, Pergamon Press, 1983. pp. 3–6.
7. Ashby, M. & Stoffell, B. Therapeutic ratio and defined phases: proposal of an ethical framework for palliative care. *Br Med J* 1991, **302**: 1322–1324.
8. Thompson, I. Ethical issues in palliative care. In: Doyle D. (ed.) *Palliative Care: The Management of Far Advanced Illness*. London, Croom Helm, 1984. pp. 461–485.
9. George, R.J.D. Palliation in AIDS – where do we draw the line? *Genitourinary Med* 1991, **67**: 85–86.
10. Saunders, C. *Hospice and Palliative Care, an Interdisciplinary Approach*. Edward Arnold, London, 1990.
11. Cartwright, A., Hockley, L. & Anderson, J.L. *Life after Death*. Routledge, London, 1973.
12. Stephany, T.M. AIDS does not fit the cancer model of hospice care. *Am J Hosp Pall Care* 1992, Vol. 9. Jan/Feb 13–14.
13. Kierny, M. The Hospice Movement bringing the soul back into medicine. *Br Med J* 1990, **83**: 3–4.
14. Wilkes, E. *Terminal Care. Report of a Working Group*. HMSO, London, 1980.
15. Ford, G. Specialist medical training in the UK. *Pall Med* 1988, **2**: 147–157.
16. Twycross, R.G. Cancer pain: a global perspective. In: Twycross, R.G. (ed.) *The Edinburgh Symposium on Pain Control and Medical Education*. RSM Services Ltd, London, 1989. pp. 3–16.
17. Winkelstein, W. & Johnson, A.M. Epidemiology overview. *AIDS* 1990, **4** (Suppl 1): 595–597.

18. George, R.J.D. The hospice movement and HIV. *Pall Med* 1993 (in press).
19. Tate, T. Palliative medicine: its content and training. *Br J Hosp Med* 1990, 44: 140–141.
20. Wilmont, B. & Hillier, R. Terminal care, present services and future priorities. *Br Med J* 198, 283: 595–598.
21. Daly, A. Training in palliative medicine. *Pall Med* 1991, 5: 303–306.
22. Saunders, C. What's in a name? *Pall Med* 1987, 1: 57–61.
23. Association of Palliative Medicine. Secretariat: Royal South Hants Hospital, Brinton's Terrace, Southampton SO2 0AJ, UK.
24. Hillier, R. Palliative medicine a new speciality. *Br Med J* 1988, 297: 874–875.
25. Doyle, D. Education and training in palliative care. *J Pall Care* 1987, 2: 5–7.
26. Weissman, D.E. Palliative medicine education: bridging the gap between acute care and hospice. *J Cancer Educ* 1991, 6: 67–68.
27. Oliver, D. Training in knowledge of terminal care in medical students and junior doctors. *Pall Med* 1989, 3: 293–297.
28. Palliative Medicine Curriculum. Association for Palliative Medicine, 11 Westwood Road, Southampton, Hants SO2 1DL, UK.
29. *Health Service Development: Terminal Care*. Health Publications Unit, Heywood, Lancashire, 1987 (HC/87/4 & LAC/87/2).
30. *Directory of Hospice Services in the UK and Republic of Ireland*. St Christopher's Hospice, Sydenham, London, 1992.
31. Bates, T. St Thomas's Hospital Terminal Care Support Team – a new concept in hospital care. *Lancet* 1978, i: 1120–1203.
32. Hockley, J.M., Dunlop, R. & Davis, R.J. Survey of distressing symptoms in dying patients and their families in hospital and the response to a symptom control team. *Br Med J* 1988, 296: 1715–1717.
33. Herxheimer, A., Begent, R., McLain, D., Phillips, L., Southcott, B. & Walton, I. The short life of the terminal care support team: experience at Charing Cross Hospital. *Br Med J* 1985, 290: 1877–1879.
34. Dunlop, R.J. & Hockley, J.M. *Terminal Care Support Teams – the Hospital Hospice Interface*. Oxford University Press, Oxford, 1990.
35. Wilkes, E. National terminal care policy – report of a working party on terminal care. *J R Soc Gen Pract* 1980, 30: 466–471.
36. Kierny, M. Changing ideas in health care. In: Seedhouse, D. & Kripp, A. (eds.) *Hospice Medicine*. John Wiley and Sons, London, 1989, pp. 1–10.
37. Parkes, C. Terminal care: home, hospital or hospice? *Lancet* 1985, i: 155–157.
38. Townsend, J., Frank, A.O., Fermont, D. *et al.* Terminal cancer care and patients' preference for place of death: a prospective study. *Br Med J* 1990, 301: 415–417.
39. Wilkes, E. Dying now. *Lancet* 1984, 1: 950–952.
40. Hobbs, T. (ed.) *Experimental Training – Practical Guidelines*. Tavistock Routledge, London, 1992.
41. Raymond Selby, G. Spiritual care of the dying patient. *Ethics Med* 1989, 5: 38–40.
42. Royal College of Physicians. Palliative care. Guidelines for good practice and audit measures. *J R Coll Phys London* 1991, 25: 325–328.

Management Strategy

43. George, R.J.D. Palliation or cure? Applying a philosophy of care in the dying. *AIDS* 1993, (Submitted for publication).
44. Levy, M.H. Effective integration of pain management into comprehensive cancer care. *Postgrad Med J* 1991, 67 (Suppl. 2): S35–S43.
45. Glick, J.H. Palliative chemotherapy: Risk/benefit ratio. In: Cassileth, B.R. & Cassileth, P.A. (Eds.) *Clinical Care of the Terminal Cancer Patient*. Lea & Febiger, Philadelphia, 1982, pp. 43–64.

46. Slevin, M.L., Stubbs, L., Plant, H.J. *et al.* Attitudes to chemotherapy: comparing views of patients with cancer with those of doctors, nurses, and general public. *Br Med J* 1990, 300: 1458–1460.
47. Anderson, J., George, R.J.D., Weller, I.V.D., Lucas, S.B. & Miller, R.F. Clinico-pathological conference. Complications of treatment for cryptosporidial diarrhoea. *Genitourinary Med* 1991, 67: 156–161.
48. Kearsley, J.H. Cytotoxic chemotherapy for common adult malignancies: the emperor's new clothes revisited? *Br Med J* 1986, 293: 871–876.
49. Lane, D.A., & Hutchinson, T.A. The notion of 'acceptable risk': the role of utility in drug management. *J Chron Dis* 1987, 40: 621–625.

Issues of Clinical Practice

50. George, R.J.D. Death anxiety – trying to make sense of it all. *AIDS* 1992, 6: 1037–1038.
51. Cassidy, S. Emotional distress in terminal cancer: discussion paper. *J R Soc Med* 1986, 79: 717–720.
52. Gilhooly, M.L.M., Berkeley, J.S., McCann, K., Gibling, F. & Murray, K. Truth telling with dying cancer patients. *Pall Med* 1988, 2: 64–71.
53. Sutherland, H.J., Llewelyn-Thomas, H.A., Lockwood, G.A., Trichter, D.L. & Till, J.E. Cancer patients: their desire for information and participation in treatment decisions. *J R Soc Med* 1989, 82: 260–263.

Audit and Quality of Life

54. Calman, K.C. Quality of life in cancer patients – an hypothesis. *J Med Ethics* 1984, 10: 124–127.
55. Timothy, A.R. Cost versus benefit in non-surgical management of patients with cancer. *Br Med J* 1988, 297: 471–472.
56. Stoll, B.A. Choosing between cancer patients. *J Med Ethics* 1990, 16: 71–74.
57. Karnofsky, D.A. & Burgenel, J.H. The clinical evaluation of chemotherapeutic agents in cancer. In: McLeod, C.M. (ed.) *Evaluation of Chemotherapeutic Agents in Cancer*. New York, Columbia University Press, 1949, pp. 141–205.
58. Priestman, T.J., & Baum, M. Evaluation of quality of life in patients receiving treatment for advanced breast cancer. *Lancet* 1976, i: 899–901.
59. Spitzer, W.O., Dobson, A.J. & Hall, J. The QL index. *J Chron Dis* 1981, 34: 585–597.
60. Cip, S., Shag, C.C., Heinrich, R.L. & Gans, B.A. Cancer inventory of problem situation: an instrument for assessing cancer patients. Rehabilitation needs. *J Psychosoc Oncol* 1983, 1: 4–10.
61. Zignand, A.S. & Snaith, R.P. The hospital and anxiety and depression scale. *Acta Psychiatr Scand* 1983, 67: 361–370.
62. Morrow, G.R., Chiarello, R.J. & Deragartis, L.R. New scale for assessing patients' psychosocial adjustment to medical illness. *Psychol Med* 1978, 8: 605–610.
63. Clark, A. & Fallowfield, L.J. Quality of life measurements in patients with malignant disease – a review. *J R Soc Med* 1986, 79: 165–169.
64. Higginson, I., Wade, A. & McCarthy, M.A. A comparison of four outcome measures of terminal care. In: Gilmore, S. (ed.) *A Safer Death: Multidisciplinary Aspects of Terminal Care*. Plenum, New York, 1989, pp. 205–211.
65. Butter, E., Higginson, I., George, R.J.D. & McCarthy, M. Palliative care for people with HIV/AIDS: views of patients, carers and providers. *AIDS Care* 1993, 5 (in press).
66. Butters, E., Higginson, I., George, R.J.D., Smits, A. & McCarthy, M. Assessing the symptoms, anxiety and practical needs of HIV/AIDS patients receiving palliative care. *Qual Life Res* 1992, 1: 47–51.

Issues of Clinical Practice

67. Aulton, N. *Pain, an Exploration*. Darton, Longman and Todd, London, 1986.
68. Buckman, R. *I Don't Know What to Say . . .* Macmillan, London, 1990.

Pain

69. Twycross, R.G. & Lack, A.S. *Symptom Control in Far Advanced Cancer: Pain Relief*. Pitman, London, 1983.
70. Hanks, G.W., Hoffbrand, B.I. & Miller, A.J. (eds) Pain control. *Postgrad Med J* 1991, **67** (Suppl. 2).
71. Bonica, J.J. Treatment of cancer pain: current status and future needs. In: Fields, H.L., Dubner, R. & Cervero, F. (eds) *Advances in Pain Research and Therapy*, Vol.9. Raven, New York, 1985, pp. 589–616.
72. Moss, V. Palliative care in advanced HIV disease: presentation, problems and palliation. *AIDS* 1990, **4**: S235–S242.
73. Dixon, P. & Higginson, I. AIDS and cancer pain treated with slow release morphine. *Postgrad Med J* 1991, **67** (Suppl. 2): S92–S94.
74. Robinson, V.H., George, R.J.D., Howes, G. & Edwards, D. Symptoms profile in late HIV disease. *VII International Conference on AIDS Florence*, Italy, June 1992, Abstract MC3160.
75. O'Brien, T., Kelly, M. & Saunders, C. Motor neurone disease: a hospice perspective. *Br Med J* 1992, **304**: 471–473.
76. Jorgensen, L., Mortensen, N.-B., Jennson, N.-H. & Erikson, J. Treatment of cancer pain patients in a multidisciplinary pain clinic. *Pain Clinic* 1993, **83**–89.
77. Ventafridda, V., Tamburini, M., Caraceni, A., De Conno, F. & Naldi, F.A. A validation study of the WHO method of cancer pain relief. *Cancer* 1987, **59**: 851–856.
78. Geyman, J. The family as the object of care in family practice. *J Family Pract* 1977, **5**: 571–575.
79. Engel, G.L. 'Psychogenic' pain and the pain prone patient. *Am J Med* 1959, **26**: 899–918.
80. Saunders, C. The nature and management of terminal pain. In: Shotton, E. (ed.) *Matters of Life and Death*. Darton Longman and Todd, London, 1970. pp. 15–25.
81. Davidson, P. Facilitating coping with cancer pain. *Pall Med* 1988, **2**: 107–114.
82. Hanks, G.W. & Justins, D.M. Cancer pain: management. *Lancet* 1992, **339**: 1031–1036.
83. Hoskin, P.J. Scientific and clinical aspects of radiotherapy in the relief of bone pain. *Cancer Survey* 1988, **7**: 69–86.
84. Portenoy, R.K. Cancer pain: pathophysiology and syndromes. *Lancet* 1992, **339**: 1026–1031.
85. Cassel, E.J. The nature of suffering and the goals of medicine. *N Engl J Med* 1982, **306**: 639–645.
86. Duggan, A.W. & Wiere, E. Central transmission of impulses in the nociceptors. Events in the superficial dorsal horn. In: Basbaum, A.L. & Besson, J.M. (eds) *Towards a New Pharmacotherapy of Pain*. New York, Wiley, 1991, pp. 35–67.
87. Evans, C.J., Helen, D.L. & Frederickson, C.K. The opioid peptides. In: Pastanack, G.W. (ed.) *The Opiate Receptors*. Clifton, New York, Humana, 1988, pp. 23–74.
88. Duggan, A.W. & North, R.A. Electrophysiology of opioids. *Pharmacol Rev* 1983, **35**: 219.
89. Yuge, O., Matsumoto, M., Kitahata, L.M., Collins, J.G. & Senami, M. Direct opioid application to peripheral nerves does not compound action potentials. *Anaesth Analg* 1985, **64**: 667.
90. Payne, R. Role of epidural and intrathecal narcotics and peptides in the management of cancer pain. *Med Clin N Am* 1987, **71**: 313–328.
91. Field, H.L. (ed.) *Pain Syndromes in Neurology*. Butterworth, Guildford, 1990.
92. Kori, S.H., Foley, K.M. & Posner, J.B. Brachial plexus lesions in patients with cancer: 100 cases. *Neurology* 1981, **31**: 45–50.
93. Arner, S. & Myerson, B.A. Lack of analgesic effect on opioids on neuropathic and idiopathic forms of pain. *Pain* 1988, **33**: 11–23.
94. Portenoy, R.K. Adjuvant analgesics. In: Doyle, D., Hanks, G.W. & MacDonald, R.N. (eds) *Oxford Textbook of Palliative Medicine* Oxford. University Press, Oxford 1993 (in press).
95. Portenoy, R.K. Issues in the management of neuropathic pain. In: Basbaum, A.I. & Besson, J.M. (ed.) *Towards a New Pharmacotherapy of Pain*. Wiley, Chichester, 1991, pp. 393–414.
96. Hanston, P., Everard, P., Mahieu, P. et al. Flecainide associated interstitial pneumonitis. *Lancet* 1991, **337**: 371–372.
97. Sinnott, C., Edmonds, P., Cropley, I. & Hanks, G. Flecaidine in cancer nerve pain. *Lancet* 1991, **i**: 1347.
98. Dunlop, R.J., Hockley, J.M., Tate, T. & Turner, P. Flecaidine in cancer nerve pain. *Lancet* 1991, **i**: 1347.
99. Clonidine reference. *Lancet* 1987, **i**: 1034.
100. Redmond, J., Fried, K.E. & Cornett, P. Clinical usefulness of an algorithm for the early diagnosis of spinal metastatic disease. *J Clin Oncol* 1988, **6**: 154–157.
101. Bowsher, D. Neurogenic pain syndromes and their management. *Br Med Bull* 1981, **47**: 644–646.
102. Tusk, R. Problem of deafferentation pain in the management of patients with cancer. *J Pall Care* 1987, **2**: 8–13.
103. Bruera, E., Rocka, E., Cedaro, L., Carraro, S. & Shackon, R. Action of oral methylprednisolone in terminal cancer patients: a prospective randomised double blind study. *Cancer Treatment Rep* 1985, **69**: 751–754.
104. Kanner, R., Martini, N. & Foley, K.M. Nature and incidence of post thoracotomy pain. *Proc Am Soc Clin Oncol* 1982, **i**: 152–156.
105. Watson, C.P.N., Evans, R.J. & Watt, V.R. The post-mastectomy pain syndrome and the effect of topical capsaicin. *Pain* 1989, **38**: 177–186.
106. Thomas, J.E., Cascino, T.L. & Earl, J.D. Differential diagnosis between radiation and tumour plexopathy of the pelvis. *Neurology* 1985, **35**: 1–7.
107. Arner, S. & Meyersin, B.A. Lack of analgesic effect of opioids on neuropathic and idiopathic forms of pain. *Pain* 1988, **33**: 11–23.
108. Saunders, C. The philosophy of terminal care. In: Saunders, C. (ed.) *The Management of Terminal Malignant Disease*. London, Edward Arnold, 1984, pp. 232–241.
109. Ventafridda, V. Continuing care: a major issue in cancer pain management. *Pain* 1989, **36**: 127–143.
110. Jennett, S., Barker, J.G. & Forrest, J.B. A double blind controlled study of the effects on respiration of pentazocine, phenoperidine and morphine in normal man. *Br J Anaes* 1968, **40**: 864.
111. Hanks, G.W., Hoffbrand, B.I. & Miller, A.J. (eds.) Pain control. *Postgrad Med J* 1991, **67** (Suppl 2).
112. Duthie, D.J.R. & Nimmo, W.S. Adverse effects of opioid analgesics. *Br J Anaes* 1987, **59**: 61–77.
113. Fields, H.L., Emerson, P.C., Leigh, B.K., Gilbert, R.F.T. & Iversen, L.L. Multiple opiate receptor sites on primary afferent fibres. *Nature* 1980, **284**: 351–353.
114. Pleuvery, B.J. An update on opioid receptors. *Br J Anaes* 1983, **55**: 143S.
115. Jordan, C. Current views on the mechanisms of opiate analgesia and some novel approaches to analgesic drugs. *Anaesthesia Review* 1984, No. 2. Churchill Livingstone, Edinburgh. 1984, p.108–136.
116. Bonica, J.J. Treatment of cancer pain: current status and future needs. In: Fields, H.L., Dubner, R. & Cervero, F. (eds.) *Advances in Pain Research and Therapy*, Vol. 9. Raven Press, New York, 1985, pp. 589–616.
117. Duthie, D.J.R. & Nimmo, W.S. Adverse effects of opioid analgesics. *Br J Anaes* 1987, **59**: 61–77.
118. Twycross, R.G. Opioid analgesics in cancer pain: current practice and controversies. *Cancer Survey* 1988, **7**: 29–53.
119. Hanks, G.W. Opioid responsive and opioid non responsive pain in cancer. *Br Med Bull* 1981, **47**: 718–731.
120. Pourtenoy, R.K., Foley, K.M. & Inturrisi, C.E. The nature of opioid responsiveness and its implications for neuropathic pain: new hypotheses derived from studies of opioid infusions. *Pain* 1990, **43**: 273–286.

121. Walker, V.A., Dicks, B. & Webb, P. Pain assessment charts in the management of chronic pain. In: Twycross, R.G. (ed.) *The Edinburgh Symposium on Pain Control and Medical Education*. Royal Society of Medicine, London, 1989, pp. 48–54.
122. Hanks, G.W. Controlled release morphine (MST Contin) in advanced cancer: the European experience. *Cancer* 1989, **623**: 2378–2382.
123. Jaffe, J.H. & Martin, W.R. Opioid analgesics and antagonists. In: Goodman-Gilman, A., Giman, L.S., Rall, T.W. & Murad, F. (eds). *The Pharmacological Basis of Therapeutics*. Pergamon, New York, 1985, pp. 485–521.
124. Reuben, A. & Winston, J. The role of the vestibular apparatus in the production of nausea and vomiting following administration of morphine to man. *J Clin Invest* 1950, **29**: 1261–1267.
125. Nimmo, W.S., Heading, R.C., Wilson, J., Toothill, P. & Prescott, L.F. Inhibition of gastric emptying by and drug absorption by narcotic analgesics. *Br J Clin Pharmacol* 1975, **2**: 509–510.
126. Champion, M.C., Sullivan, S.N., Chamberlain, M. & Vezina, N. Naloxone and morphine inhibit gastric emptying of solids. *Can J Physiol Pharm* 1982, **60**: 732–735.
127. Lechin, F., van der Dijk, B. & McArthur, K.E. Opposite effects on human distal colon motility of two postulated alpha 2 antagonists (Meyanserine and Chlorprothixene) and one alpha 2 agonist (clonidine). *J Clin Pharm* 1983, **23**: 209–215.
128. Anderson, D.S., Durbin, T.E., Orloff, M.J. & Dharmasathaphon, K. Clonidine and Lidamide to inhibit watery diarrhoea in a patient with lung cancer. *Ann Intern Med* 1982, **96**: 323–328.
129. Jennett, S., Barker, J.G. & Forrest, J.B. A double blind controlled study of the effects on respiration of pentazocine, phenoperidine and morphine in normal man. *Br J Anaes* 1968, **40**: 864.
130. Ghodse, A.H. & Creighton, F.J. Opioid analgesics – narcotic antagonists. In: Dukes, M.N.G. (ed.) *Myler's Side Effects of Drugs*, 11th ed. Amsterdam, Elsevier, 1988, pp. 137–155.
131. Hammond, J.E. Reversal of opioid-associated late onset respiratory depression by nalbuphine hydrochloride. *Lancet* 1984, **2**: 1208.
132. Snier-Mor, I., Weinstock, M., Davidson, J.T. & Bahar, M. Physostigmine antagonises morphine-induced respiratory depression in human subjects. *Anaesthesiology* 1983, **59**: 6–9.
133. Hanks, G.W., Twycross, R.G. & Lloyd, J.W. Unexpected complication of successful nerve block. *Anaesthesia* 1981, **36**: 37–39.
134. Hanks, G.W. & Twycross, R.G. Pain: the physiological antagonist of opioid analgesics. *Lancet* 1984, **i**: 1477–1478.
135. Murray, P. Prevention of urinary retention with phenoxybenzamine during epidural morphine. *Br Med J* 1984, **288**: 645–646.
136. Porter, E.J.B. & Jick, H. Addiction rare in patients treated with narcotics. *N Engl J Med* 1980, **302**: 123.
137. Enck, R. Understanding tolerance, physical dependence and addiction in the use of opioid analgesics. *Am J Hospice Pall Care* 1991, **8**: 1–15.
138. Portenoy, R.K. & Foley, K.M. Chronic use of opioid analgesics in non-malignant pain: report of 38 cases. *Pain* 1986, **25**: 171–186.
139. Taub, A. Opioid analgesics in the treatment of chronic intractable pain of non-neoplastic origin. In: Kitahata, L.M. & Collins, J.D. (eds) *Narcotic Analgesics in Anaesthesiology*. Williams and Wilkins, Baltimore, 1982, pp. 199–208.
140. Warfield, C.A. Guidelines for the use of MS Contin tablets in the management of cancer pain. *Postgrad Med J* 1991, **67**: S9–S13.
141. Hanks, G.W. Morphine pharmacokinetics and analgesia after oral administration. *Postgrad Med J* 1991, **67**: S60–S63.
142. Moulin, D.E., Kreeft, J.H., Murray-Parsons, N. & Bouquillon, A.I. Continuous subcutaneous and intravenous infusions of Hydromorphone compared for management of cancer pain. *Lancet* 1991, **337**: 465–468.
143. Jones, B.A. & Hanks, G.W. Modes of drug administration, longer lasting syringe drivers running in over 37 days. *Br Med J* 1986, **292**: 1496.
144. Rippamonte, C. Use of transdermal and inhaled opioids. *Pall Med* 1992, **6**: 98–104.
145. Morgan, M. The rational use of intrathecal and extradural opioids. *Br J Anaes* 1989, **63**: 165–188.
146. Gonzalez Navarro, A. Cancer pain and intrathecal morphine. *Pall Med* 1989, **3**: 287–292.
147. Hogan, Q., Haddox, J.D., Abram, S., Weissman, D., Taylor, M.L. & Janjan, N. Epidural opiates and local anaesthetics for the management of cancer pain. *Pain* 1991, **46**: 271–279.
148. Hill, H.F., Chapman, C.R., Kornell, J., Sullivan, K., Saeger, L. & Beneditti, C. Self administration of morphine in bone marrow transplant patients reduces drug requirement. *Pain* 1990, **40**: 121–129.
149. McNamara, P., Minton, M. & Twycross, R.G. Use of midazolam in palliative care. *Pall Med* 1991, **5**: 244–249.
150. Epstein, J.B., Stephenson-Moore, P. & Jackson, S. Prevention of oral mucositis in radiation therapy: a controlled study with benzylamine hydrochloride rinse. *J Radiation Oncol Biol Physics* 1989, **6**: 1571–1575.
151. Jepson, B.A. Relieving the pain of pressure sores. *Lancet* 1992, **339**, **i**: 503–504.
152. Lynn, B. Capsaicin: actions on nociceptive C-fibres and therapeutic potential. *Pain* 1990, **41**: 61–69.
153. Wells, J.C.D. The use of nerve destruction for relief of pain in cancer: a review. *Pall Med* 1989, **3**: 239–247.
154. Hardy, P.A.T. The role of the pain clinic in the management of the terminally ill. *Br J Hosp Med* 1990, **43**: 42–46.
155. Sharfman, W.H. & Walsh, T.D. Has the analgesic efficacy of neurolytic coeliac plexus block been demonstrated in pancreatic cancer pain? *Pain* 1990, **41**: 267–271.
156. Tasker, R.R. Management of nociceptive deafferentation and central pain by surgical intervention. In: Fields, H.L. (ed.) *Pain Syndromes in Neurology*. Butterworth, London, 1990, pp. 143–200.
157. Gallasgo, C.S.B. The role of the orthopaedic surgeon in the treatment of bone pain. *Cancer Surveys* 1988, **7**: 102–125.
158. Cousins, N. Anatomy of an illness (as perceived by the patient). *N Engl J Med* 1976, **295**: 1458–1463.
159. Ramsey, N. Psychiatric problems work with liaison psychiatrist – referrals from a palliative care unit. *Pall Med* 1992, **6**: 54–60.
160. Stedford, A. & Blocks, S. The psychiatrist in the terminal care unit. *Br J Psych* 1979, **135**: 1–6.
161. Zborovski, N. Cultural components in response to pain. *J Soc Issues* 1952, **8**: 16–30.
162. Elton, D., Burroughs, D. & Stanley, G.V. Hypnosis and chronic pain. *Aust J Clin Exp Hyp* 1980, **18**: 160–180.
163. Meichenbaum, D. & Turk, D. Stress: preparation techniques. The cognitive – behavioural management of anxiety, anger and pain. In: Davidson, P.O. (ed.) *The Behavioural Management of Anxiety, Depression and Pain*. Brunner/Mazel, New York, 1976, pp. 1–34.
164. Melzack, R. & Perry, C. Self regulation of pain: the use of alpha feedback and hypnotic training for the control of chronic pain. *Exp Neurol* 1975, **46**: 452–469.
165. Connell, C. Art therapy as part of a palliative care programme. *Pall Med* 1992, **6**: 18–23.

Breathlessness

166. DeConno, F., Spoldi, E., Caraceni, A. & Ventafridda, V. Does pharmacological treatment affect the sensation of breathlessness in terminal cancer patients? *Pall Med* 1991, **5**: 237–243.

167. Horn, L.V. Terminal dyspnoea – a hospice approach. *Am J Hospice Pall Care* 1992, 9: 24–33.
 168. Heyse-Moore, L.H., Ross, V. & Mullee, M.A. How much of a problem is dyspnoea in advanced cancer? *Pall Med* 1991, 5: 20–26.
 169. George, R.J.D., Robinson, V.H., Howes, G. & Edwards, D. Factors influencing choice and place of death in patients with AIDS. *VII International Conference on AIDS*. Florence, Italy, 1991, Abstract Book No: WD4063.
 170. Ripamonti, C. & Bruera, E. Transdermal and inhalatory routes of opioid administration: the potential application in cancer pain. *Pall Med* 1992, 6: 98–104.
 171. Light, R.W., Muro, J.R. & Sato, R.I. Effects of oramorphine on breathlessness and exercise tolerance in patients with chronic obstructive pulmonary disease. *Am Rev Resp Dis* 1989, 139: 126–133.
 172. Cohen, M.H., Anderson, A.J. & Krasnow, S.H. Continuous intravenous infusion of morphine for severe dyspnoea. *South Med J* 1991, 84: 229–234.
 173. Woodcock, A.A., Gross, E.R. & Geddes, D.M. Drug treatment of breathlessness: contrasting effects of diazepam and promethazine in pink puffers. *Br Med J* 1982, 283: 343–346.
 174. Stark, R.D., Gambles, S.A. & Lewis, J.A. Methods to assess breathlessness in healthy subjects: a critical evaluation and application to analyse the acute effects of diazepam and promethazine on breathlessness induced by exercise or by exposure to raised levels of CO₂. *Clin Sci* 1981, 61: 429–439.
 175. Santolicandro, A.L., Petrucci, S. & Guitini, C. Effects of Lidocaine aerosol on dyspnoea in emphysematous patients. *Clin Resp Physiol* 1983, 19: 41–42P.
 176. Winning, A.J., Hamilton, R.D., Shea, S.A., Knott, C. & Guz, A. The effect of airway anaesthesia on the control of breathing and the sensation of breathlessness in man. *Clin Sci* 1985, 68: 215–225.
 177. De Conno, F., Spoldi, E. & Ventafriedda, V. Does pharmacological treatment affect the sensation of breathlessness in terminal cancer patients. *Pall Med* 1991, 5: 237–243.
 178. Howard, P. Lignocaine aerosol and persistent cough. *Br J Dis Chest* 1977, 71: 19–24.
 179. Johanson, G.A. Use of anticholinergics in palliative care. *Am J Hospice Pall Care* 1992, 9: 1–3.
- Constipation**
180. Twycross, R.G. & Lack, S.A. *Control of Alimentary Symptoms in Far Advanced Cancer*. Churchill Livingstone, Edinburgh, 1986.
 181. Twycross, R.G. & Harcourt, J.M.V. The use of laxatives at a palliative care centre. *Pall Med* 1991, 5: 27–33.
 182. Sykes, N.P. A clinical comparison of laxatives in a hospice. *Pall Med* 1991, 5: 307–314.
 183. Sykes, N.P. Oral naloxone in opioid associated constipation. *Lancet* 1991, 337: 1475.
 184. Basilisco, G., Camboni, G., Bozzani, A., Paravicini, M. & Bianchi, P.A. Oral naloxone antagonises loperamide-induced delay of oro-caecal transit. *Dig Dis Sci* 1987, 32: 829–832.
 185. Baines, M., Oliver, D.J. & Carter, R.L. Medical management of intestinal obstruction in patients with advanced malignant disease, a clinical and pathological study. *Lancet* 1985, 2: 990–993.
 186. De Conno, F., Caraceni, A., Zecca, E., Spoldi, E. & Ventafriedda, V. Continuous subcutaneous infusion of hyoscine butylbromide reduces secretions in patients with gastrointestinal obstruction. *J Pain Smpt Control* 1991, 6: 484–486.
 187. Johannsen, G.A. Use of anticholinergics in palliative care. *Am J Pall Hospice Pall Care* 1992, 9: 1–3.
 188. George, R.J.D., Swire, N., Robinson, V.H., Edwards, D. & Jennings, A.L. Opiates and symptom control in end stage HIV disease. *Pall Med* 1993 (submitted).
 189. Editorial. Ocreotide steaming ahead. *Lancet* 1992, 339: 837–839.
 190. Cello, J., Grendell, J.H. & Basulk, P. Effect of octreotide on refractory AIDS associated diarrhoea. *Ann Intern Med* 1991, 115: 705–710.
 191. Landsden, F.T., Adams, D.B. & Anderson, M.C. Treatment of external pancreatic fistulas with somatostatin. *Am J Surg* 1989, 55: 695–698.
- Nausea and Vomiting**
192. Regnard, C. & Comiskey, M. Nausea and vomiting in far advanced cancer – a flow diagram. *Pall Med* 1992, 6: 146–151.
 193. Dunlop, G.M. A study of the relative frequency and importance of gastrointestinal symptoms and weakness in patients with far-advanced cancer. *Pall Med* 1989, 4: 37–43.
 194. Taylor, M.B., Moran, B.J. & Jackson, A.A. Nutritional problems and care of patients with far advanced disease. *Pall Med* 1989, 3: 31–38.
 195. Photkin Niemegeers, C.J.E. & Laduron, P.M. Pharmacology and biochemistry of haloperidol. *Proc R Soc Med* 1976, 69 (Suppl 1): 3–8.
 196. Stoll, B.A. Radiation sickness: an analysis of over 1000 controlled drug trials. *Br Med J* 1962, ii: 507–510.
 197. Schulze-Delrieu, K. Metoclopramide. *N Engl J Med* 1981, 305: 28–33.
 198. Jenner, P., Clow, A. & Reavill, C. A behavioural and biochemical comparison of dopamine receptor blockade produced by haloperidol with that produced by substituted benzamide drugs. *Life Sci* 1978, 23: 545–549.
 199. Regnard, C., Pashley, S. & Westrope, F. Antiemetic/diamorphine mixture compatibility in infusion pumps. *Br J Pharm Pract* 1986, 8: 218–220.
 200. Johnson, I. & Patterson, S. Drugs used in combination in the syringe driver – a survey of hospice practice. *Pall Med* 1992, 6: 125–130.
 201. Allwood, M.C. The stability of diamorphine alone and in combination with antiemetics in plastic syringes. *Pall Med* 1991, 5: 330–333.
 202. George, R.J.D., Robinson, V.H., Cottrill, C. *et al.* Steroids as a palliative measure in advanced, disseminated Kaposi's sarcoma. *Third Eur Conf Clinical Aspects of HIV Infection*. Paris, 1992.
 203. Jennings, A.L. & George, R.J.D. The use of corticosteroids in the palliative care of patients with late stage HIV disease. *Pall Med* 1992 (in press).
 204. Aapro, M.S. & Alberts, D.S. Dexamethasone as an antiemetic in patients treated with cisplatin. *N Engl J Med* 1981, 305: 520.
 205. Rich, W.M., Abdulhayoglu, G. & Di Saia, P.J. Methylprednisolone as an antiemetic during cancer chemotherapy. A pilot study. *Gynecologic Oncol* 1980, 9: 193–198.
 206. Cassileth, P.A., Lusk, E.J., Torri, S. *et al.* Antiemetic effectiveness of dexamethasone therapy in patients receiving chemotherapy. *Arch Intern Med* 1983, 143: 1347–1349.
 207. Markman, M., Scheidler, V., Ettinger, D.S., Shirley, A., Quaskey, B.S. & Mellits, E.D. Antiemetic efficacy of dexamethasone. *N Engl J Med* 1984, 311: 549–552.
 208. Guslandi, M., Tittobello, A., Piper, J.M., Ray, W.A. & Dougherty, J.R. Steroid ulcers: a myth revisited. *Br Med J* 1992, 304: 655–656.
 209. Piper, J.M., Ray, A.W., Daugherty, M.S. & Griffin, M.R. Corticosteroid use in peptic ulcer disease: role of non steroidal anti-inflammatory drugs. *Ann Intern Med* 1991, 114: 735–740.
 210. Carpani de Kaski, M., Levi, S., Rentsch, R. & Hodgson, H.J.F. Steroid ulcers. *Br Med J* 1992, 304: 1443–1444 (letter).
- AIDS**
211. Walsh, J.M., Barlow, D. & Richardson, P.H. Symptoms of HIV disease. *Pall Med* 1991, 5: 46–51.

212. Cole, R.M. Medical aspects of care for the person with advanced acquired immunodeficiency syndrome (AIDS): a palliative care perspective. *Pall Med* 1991, 5: 96 – 111.

Bone Disease

213. Twycross, R.G. & Fairfield, S. Pain in far advanced cancer. *Pain* 1982, 14: 103 – 110.
214. Dodwell, D. & Howell, A. Treating bony metastases. *Br Med J* 1991, 303: 429 – 430.
215. Stoll, B.A. Natural history, prognosis and staging of bone metastases. In: Stoll, B.A. & Parbhoo, S. (eds.) *Bone Metastases: Monitoring and Treatment*. Raven Press, New York, 1983, pp. 1 – 4.
216. Smith, E.I. & Macaulay, V. Comparison of different endocrine therapies in management of bone mets from breast cancer. *J R Soc Med* 1985, 78 (Suppl 9): 15 – 17.
217. Lyss, A.P. Systemic treatment for prostrate cancer. *Am J Med* 1987, 83: 1120 – 1128.
218. Price, P., Hoskin, P.J., Easton, D., Austin, D., Palmer, S.G. & Yarnold, J.R. Prospective randomised trial of single and multifraction radiotherapy schedules in the treatment of painful bony metastases. *Radiother Oncol* 1986, 6: 247 – 255.
219. Fleisch, H. & Felix, R. Diphosphonates. *Calcif Tissue Int* 1979, 27: 91 – 94.
220. Clarke, N.W., Holbrook, I.B., McClure, J. & George, N.J.R. Osteoclastic inhibition by pamidronate in metastatic prostatic cancer: a preliminary study. *Br J Cancer* 1991, 63: 420 – 423.
221. Robinson, R.G., Spicer, J.A., Preston, D.F., Wegst, A.V. & Martin, N.L. Treatment of metastatic bone pain with strontium-89. *Int J Rad Appl Instrum* 1987, 14: 219 – 222.
222. Ralston, S.H., Gallacher, S.J., Patel, U. *et al.* Comparison of three intravenous biphosphonates in cancer-associated hypercalcaemia. *Lancet* 1989, ii: 1180 – 1182.
223. Fidler, M. Incidence of fracture through metastases in long bones. *Acta Orthop Scand* 1981, 52: 623 – 627.
224. Galasko, C.S.B. Local complications of skeletal metastases. In: *Skeletal Metastases*. Butterworth, London, 1986, pp. 125 – 127.
225. Kaye, P.M. & Olliver, D.J. Hypercalcaemia in advanced malignancy. *Lancet* 1985, i: 512.
226. Wilkinson, R. Treatment of hypercalcaemia associated with malignancy. *Br Med J* 1984, 288: 812 – 813.
227. Percival, R.G., Yates, A.J.P., Grey, R.E.S., Neil, M.E., Forrest, A.R.W. & Kanis, J.A. Role of glucocorticoids in management of malignant hypercalcaemia. *Br Med J* 1984, 289: 287.
228. Ralston, S.H., Gallagher, S.J., Patel, U. *et al.* Comparison of three intravenous biphosphonates in cancer associated hypercalcaemia. *Lancet* 1989, 52: 623 – 627.

229. Malton, E.R., Cantrill, J.A., Craig, A.E., Howell, A., Davis, M. & Anderson, D.C. Single dose versus daily IV aminohydroxypropyladene biphosphonate (APD) for hypercalcaemia malignancy. *Br Med J* 1988, 296: 811 – 814.

Invasive Procedure

230. Valouri, R.M. & Dover, S. Palliative gastrointestinal endoscopy. *Pall Med* 1988, 2: 101 – 106.
231. Cox, J. & Bennett, J.R. Light at the end of the tunnel? Palliation for oesophageal carcinoma. *Gut* 1987, 28: 781 – 785.
232. Ogilvie, A.L., Dronfield, M.W., Ferguson, R. & Atkinson, M. Palliative intubation of oesophago-gastric neoplasms at fiberoptic endoscopy. *Gut* 1982, 23: 1060 – 1067.
233. Barr, H., Krasner, N., Raouf, A. & Walker, R.J. Laser therapy or intubation for palliation of malignant dysphagia? *Gut* 1987, 28, A 1358.
234. Sarr, M.G. & Cameron, J.L. Surgical palliation of unresectable carcinoma of the pancreas. *World J Surg* 1984, 8: 906 – 918.
235. Pitt, H.A., Cameron, J.L., Posterior, R.G. & Cadacz, T.R. Factors affecting mortality in biliary tract surgery. *Am J Surg* 1981, 141: 66 – 71.
236. Ferucci, J.T. & Mueller, P.R. Interventional radiology of the biliary tract. *Gastroenterology* 1982, 82: 974 – 985.
237. Speer, A.G., Cotton, P.B., Russell, R.C.G., Mason, R.R. & Hatfield, A.R.W. Randomised trial of endoscopic vs percutaneous stent insertion in malignant obstructive jaundice. *Lancet* 1987, ii: 57 – 62.
238. Hetzel, M.R. Laser palliation of tracheobronchial tumours – a review. *Pall Med* 1988, 2: 134 – 138.
239. George, P.J.M., Garrett, C.P.O. & Hetzel, M.R. Role of the Nd-yag Laser in the management of tracheal tumours. *Thorax* 1987, 42: 440 – 444.

Terminal Phase

240. Holden, C.M. Anorexia in the terminally ill cancer patient, the emotional impact on a patient and family. *Hospice J* 1991, 7: 73 – 84.
241. Aynesbury, M. The use of subcut midazolam in the home care setting. *Pall Med* 1989, 3: 299 – 301.
242. De Sousa, E. & Jepson, B.A. Midazolam in terminal care. *Lancet* 1988, 1: 67 – 68.
243. Cameron, N.M.deS. *Death without Dignity. Euthanasia in Perspective*. Rutherford House, Edinburgh. 1990.
244. Rachels, J. *The End of Life: Euthanasia and Morality*. Oxford University Press, Oxford. 1986.
245. Ahronheim, J.C. & Gasner, M.R. The sloganism of starvation. *Lancet* 1990, 335: 278 – 279.