New Drugs

Controlling symptoms in advanced cancer

T D WALSH, T S WEST

Many patients who have cancer have metastatic disease at diagnosis and cannot be cured by modern cancer treatment, though there are tumours—for example, tumours of the testis, choriocarcinomas, and Hodgkin's disease—that are now curable even at an advanced stage. Some other tumours—for example, in the lung (oat cell), breast, and prostate—may show considerable benefit from chemotherapy or hormonal manipulation. This is why histological proof of diagnosis should always be obtained and management reviewed by an oncologist.

Many patients who have cancer present with pain or other symptoms, and for them the need for relief from symptoms occurs throughout the course of the disease and not just in the terminal stages. Those patients who are unfortunate enough to have an incurable cancer will often die within two years after metastatic disease has been diagnosed.

Early in treatment of the disease priority must be given to attempts to obtain a cure. For patients who have advanced cancer, however, the symptoms are the illness. A decision must then be made that the disease is incurable and that henceforth the priorities of management must focus on controlling the symptoms. Once this has been decided, medical and nursing care can aim positively at relieving distress. Recognising that "the symptoms are the disease" is an important psychological adjustment for both the doctor and the patient. It helps to avoid the "nothing more can be done" syndrome or the continuation of ineffective treatments. Implicit in this decision is tactful honesty and open communication among the patient, doctor, and family.

Principles of controlling symptoms

Studies have repeatedly shown that the control of pain and other symptoms is only too often inadequate. Many doctors (including oncologists) have received no training in caring for dying patients. Some feel helpless and inadequate, with predictable effects on care of the patient. Dying patients are still commonly ignored during ward rounds or placed in a side room.

Success in controlling symptoms lies in time honoured medical care allied with detailed attention to therapeutics. Many doctors who are faced with a patient who has advanced cancer abandon the problem solving diagnostic approach that they use in managing other medical disorders, but it is essential to retain such an approach for the optimal management of symptoms. Taking a careful history of the patient's complaints should be followed by a detailed problem oriented physical examination. Invasive diagnostic procedures—for example, taking blood—or other time consuming actions should be kept to a minimum.

Advanced cancer is an acute disease—the clinical picture may change rapidly, so patients must be reassessed regularly and plans for treatment and drugs adjusted. First rate nursing care is essential; fortunately, most nurses see this type of work as a professional challenge. Drugs must be constantly reviewed to avoid iatrogenic problems contributing to the patients' misery.

Many of the principles learnt in this type of work are relevant to other incurable diseases—for example, cystic fibrosis and emphysema. We shall not deal with children who have advanced cancer, but the principles and practices are similar, with appropriate reductions in drug dosage. Most patients' symptoms can be controlled most of the time by the proper use of a few well known drugs.

Pain

Pain is the most dreaded symptom of advanced cancer. It is due to destruction by the tumour of organs, bones, or nerves and increases in frequency and severity as the disease progresses. Pain is almost always associated with a solid tumour or multiple myeloma, being uncommon in the lymphomas and leukaemias. Patients commonly have several sites of disease and multiple pains.

The probable cause of each pain should be diagnosed and the greatest attention directed to the pain causing the most distress or incapacity. No patient who has cancer should die in unrelieved pain; the means of obtaining good control of pain are available to any competent medical practitioner.

Pain that is difficult to control occurs in about 5-10% of patients. Emotional and family problems are important. Pain due to extensive bone metastases or pain in young patients may present problems. Such patients may need to be referred to a pain clinic, hospice, or symptom control team.

Opioids

The specific opioid used is often less important than the manner in which it is used. The best results are obtained by giving the drugs orally, tailoring every dose individually by titrating it against the pain, and giving the drug regularly (usually every four hours). Dosing round the clock—that is, giving scheduled doses even when there is no pain—is a key concept.

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A second key concept in using opioids is the use of "rescue" analgesics for breakthrough pain, in which the patient is instructed to take a predetermined dose of analgesic should pain intervene before a dose of a scheduled drug is due. The drug used as a rescue can be as simple as paracetamol 500-1000 mg or perhaps 10-25% of the current dose of opioid given by mouth every four hours. Depending on the circumstances, rescue analgesics can also be given sublingually, rectally, or by injection. The dose of the rescue analgesic is adjusted according to the severity of pain breakthrough. Frequent breakthroughs act as a useful monitor to indicate the need for an increase in the regular dosage of analgesic.

Provided that these simple ideas are followed and explained clearly to the patient good control of pain can be achieved in most patients. Opioids are most effective against pain of visceral origin and relatively ineffective against pain due to bone metastases or nerve destruction. Opioids must always be accompanied by a regular laxative to prevent the otherwise inevitable constipation.

MORPHINE

Morphine is the drug of choice for chronic severe pain in advanced cancer. It is flexible and has been in use for a long time. Morphine is used like insulin in diabetes mellitus, except that instead of being titrated against the blood concentration of glucose the dose is titrated against the pain reported by the patient. Morphine in aqueous solution is given every four hours in five to six doses/24 h. The early morning (2 am) dose is omitted if sleep is not disturbed by pain and provided that the patient wakes free of pain in the morning. A common starting dose is 5-10 mg every four hours (depending on the patient's previous experience of analgesics and therapeutic response). The dosage is increased in steps (5, 10, 15, 20, 30, 45, 60, 90, 120, 160, 180 mg every four hours) until the pain is controlled.

Most patients need one of the smaller dosages to control pain. If 30 mg every four hours is ineffective it is wise to review the diagnosis and treatment to ensure that nothing has been overlooked—for example, non-steroidal anti-inflammatory drugs for painful bone metastases. If doses of 60 mg every four hours do not provide acceptable relief from pain specialist help should be considered.

Morphine has the advantage that it can also be given sublingually, rectally, and by continuous subcutaneous or intravenous infusion. Intermittent subcutaneous injection should be used only for moderate or severe breakthrough pain in patients who have reached the terminal stage and cannot swallow. Bolus intravenous injections should not be used for routine pain control, as they provide poor control of pain with maximum side effects. Every effort must be made to control pain using oral medications.

Alternative routes of administration have to be considered in those who have swallowing difficulties and fluctuating levels of consciousness. Most patients (70%) can continue to take oral drugs to within 72 hours of death. Continuous subcutaneous infusion of morphine and other opioids is a useful approach in those who have poor control of pain, are unable to swallow, or suffer from severe nausea or vomiting.

Heroin and hydromorphone are useful alternative drugs for parenteral use, as they are highly potent—that is, they have a greater analgesic effect for each mg administered. They can therefore be

given in small volumes, which are less distressing for intermittent subcutaneous or intravenous injection and more convenient for continuous infusion. Heroin, however, has no advantage over morphine in terms of its analgesic efficacy or side effects (table I).

Side effects of morphine

Provided that the oral route and tailored individual doses are followed the use of morphine as described above is safe. Respiratory depression is uncommon. Though in advanced disease relief of pain must take priority over concern about possible ventilatory impairment, this is not to say that deliberate overdosing should be contemplated. Overdosed patients become confused and restless, distressing staff and other patients. The aim of treatment is to relieve distress, not create it. It is bad ethics and poor medical practice deliberately to overdose dying patients.

Though patients may become physically dependent on opioids—that is, develop a withdrawal syndrome if the drug is abruptly withdrawn—addiction (drug seeking behaviour) is rare provided that adequate doses of opioids are given. Paradoxically, patients who request increased dosages of analgesics because they are in pain often have their dosage reduced because of ungrounded fears of addiction. Opioids can in fact be withdrawn at any time by reducing the dose in steps similar to the method used for withdrawing corticosteroids. Withdrawal symptoms after accidental withdrawal from oral opioids are surprisingly mild. Naloxone should be used only for specific indications, as it can produce a massive withdrawal syndrome with severe pain breakthrough. Tolerance—that is, a relentless increase in opioid dosage with poor control of pain—does occur but is uncommon, and its frequency and importance have been exaggerated. It does not prevent good control of pain in most patients who have cancer.

The three common side effects of opioids are constipation, nausea or vomiting, and drowsiness. Constipation is inevitable and must always be anticipated when regular administration of opioids begins. Both nausea or vomiting and drowsiness tend to be mild and transient. They often clear, even with the continued use of morphine, after a few days. An antiemetic—for example, prochlorperazine 5.0 mg orally every four hours—is often prescribed routinely for a week after morphine is started. Drowsiness is troublesome in only a few patients. It is important to review the treatment to identify other potentially sedative drugs. Excessive sedation may require a reduction in the dosage of morphine; some doctors add a stimulant—for example, amphetamine.

Severe nausea and vomiting may respond to conventional antiemetics; metoclopramide (given regularly every eight hours) is a good first choice. A change in the way morphine is given may also help. Patients nauseated by liquid morphine may do better with sustained release tablets or vice versa. If fine tuning of the dosage of morphine is required for these problems, however, this is most easily accomplished by using morphine liquid every four hours.

Sustained release morphine

Tablets for the sustained release of morphine (10, 30, 60, and 100 mg) are now available. This preparation is a considerable

TABLE I—Recommended alternatives to oral morphine

Drug	Interval between doses (hours)	Tablet	Morphine equivalent (as solution every four hours)	Comments
Diamorphine (heroin)	4	10 mg (but usually prescribed in an elixir)	10-15 mg	Identical in use with morphine. More soluble
Phenazocine (Narphen)	8	5 mg	20 mg	Useful alternative to morphine. Ceiling effect at 40-50 mg/day
Dextromoramide (Palfium)	2	5 mg (and 10 mg)	15 mg (peak effect)	Too short acting for regular use. Good for "breakthrough pain."
Oxycodone pectinate (Proladone)	8	30 mg (suppository)	15 mg	Can be given sublingually Useful if vomiting present and in the home

Taken from: Baines M. *Drug control of common symptoms*. London: St Christopher's Hospice, 1986.

practical advance. Once a patient has been stabilised with doses of liquid morphine every four hours the dosage is halved and the tablets substituted on a mg for mg basis—that is, 20 mg every four hours $\times$ six doses = 120 mg/24 hours = 60 mg of the sustained release tablets every 12 hours. The tablets must not be chewed or crushed, as this destroys the sustained release effect and can be dangerous. Some patients need to take them every eight hours, for reasons that are unclear. They are best not used for titrating morphine dosage and should be avoided in patients who have severe gastrointestinal abnormalities or swallowing difficulties.

Non-steroidal anti-inflammatory drugs

Aspirin and related drugs are used in two main ways in treating pain in cancer. Firstly, they seem to have a specific effect on pain caused by bone metastases by interfering with the production of prostaglandin. This is doubly important, as this type of pain responds poorly to opioids. For those patients who have diffuse bone metastases and in whom chemotherapy, hormonal treatments, and radiation treatment are ineffective non-steroidal anti-inflammatory drugs are the treatment of choice. (In limited painful bone metastases single dose radiation treatment is the first choice and is very effective.) Non-steroidal anti-inflammatory drugs vary in effectiveness, but gratifying responses do occur and will be seen within 48-72 hours.

Secondly, non-steroidal anti-inflammatory drugs have a general non-specific analgesic effect. The combination of one of these drugs and an opioid will provide better pain relief than either drug used alone.

The side effects of non-steroidal anti-inflammatory drugs are well known. In patients who have cancer and who are thrombocytopenic they are best avoided because of the risk of haemorrhage. There is also a confusing number of these drugs available. It is worth maximising the dosage of individual agents and changing drugs if side effects are a problem or if a poor response is obtained. Aspirin is a good drug, and many patients tolerate it well. Naproxen is a suitable alternative. Some degree of trial and error is usual, as responses and side effects vary among different non-steroidal anti-inflammatory drugs.

Psychotropic, antiepileptic, and psychostimulant drugs

Psychotropic drugs have long been used to treat various pain syndromes in both malignant and non-malignant disease. Phenothiazines and antidepressants are used alone or in combination. Treatment has been empirical, and specific indications and correct dosages are ill defined. In pain from cancer an opioid sparing action has been claimed for both groups of drugs. There is now evidence that tricyclic antidepressants do have a coanalgesic opioid sparing effect. Curiously, this action does not affect mood.

For the non-specialist who is finding it difficult to control pain in a patient who has advanced cancer, trying an antidepressant is always worth while, as depression is difficult to diagnose in a chronic physical illness. Phenothiazines are sedative, antiemetic, and possibly coanalgesic. They are also useful for helping to control anxiety and agitation in the terminal stages.

Pain due to destruction of nerves may respond to antidepressants or antiepileptic agents. Burning pain is said to respond to antidepressants, whereas stabbing pain may respond to phenytoin or carbamazepine. Psychostimulants like methylphenidate are useful in those complaining of chronic weakness or if there is excessive sedation induced by opioids.

Corticosteroids

Corticosteroids seem to help pain that is caused by the destruction of nerves—for example, damage to the brachial or lumbosacral plexus. Their mechanism of action is unknown. Relief of pain is

difficult to separate from their psychostimulating, anorectic, and strength improving actions, which are all beneficial in advanced cancer. The side effects of corticosteroids are well known and will not be described here. Many patients who have advanced cancer will not live long enough to develop serious problems, provided that dosage is carefully monitored. Most patients tolerate moderate doses well—for example, dexamethasone 4-6 mg/day.

Problems

ANOREXIA

Anorexia is a common but poorly understood complaint. Many find it as distressing as pain. In some patients who have cancer it is related to previous chemotherapy or radiation treatment and if so usually improves once this treatment has been completed. Abnormalities in the sensation of taste are common in patients who have cancer and contribute to the problem.

A dietitian should be consulted about the choice and composition of the diet. A multivitamin tablet should be given daily to those who are unable to eat normally. Megavitamin treatment is best avoided; it is ineffective and can be dangerous. There is no evidence that zinc supplements help. Patients who have cancer show a diurnal variation in appetite; their appetite is often best in the morning, and if so appropriate adjustments in the diet should be made. Changes in food preparation or additives help those with abnormalities in taste—for example, reducing salt in cooking if food tastes too salty.

Corticosteroids are very effective in anorexia, and most patients will respond to them. The disadvantage of their use is steroid side effects, which are common, though usually minor. Oral thrush should be routinely looked for and dosage adjusted for the optimal effect at the lowest dose. Alcohol is readily available and is a familiar effective appetite stimulant. Metoclopramide 10 mg orally every six hours seems specifically to help those who have symptoms of gastroparesis—that is, early satiety—but may help others too. Those who respond will be less anorectic and gain weight. Cyproheptadine may be tried if corticosteroids are ineffective, but its record is unimpressive.

NAUSEA AND VOMITING

Nausea and vomiting are common (60%) in advanced cancer, mostly in elderly women. Certain diseases are associated with an increased incidence of nausea and vomiting—namely, cancer of the breast, stomach, ovary, and pancreas and leukaemia. The precise cause is often unclear. Among those given opioids vomiting is also more common in women and is more likely to create difficulties in treatment. It is important to exclude common remediable causes such as faecal impaction. Sometimes it may be appropriate to investigate and then attempt to control uraemia or hypercalcaemia or their underlying cause.

Some patients whose vomiting is induced by opioids respond well to metoclopramide, possibly because of its action in helping gastric motility. If vomiting is severe or persistent and unresponsive to single antiemetics a combination of drugs with different sites of action—for example, metoclopramide plus prochlorperazine—should be tried. Cyclizine or an anticholinergic such as hyoscine can also be added. This approach is often effective, and there are theoretical reasons to support it.

COUGH AND DYSPNOEA

Dyspnoea is common (incidence >40%) even in patients who have cancer without obvious cardiorespiratory disease. In those who have considerable or recurrent pleural effusions and dyspnoea, thoracentesis followed by tetracycline pleurodesis can be performed if the likely survival time of the patient is weeks or months. Morphine in small doses (sustained release morphine 10 mg twice daily) is effective. Dyspnoea due to lymphangitis carcinomatosa is

difficult to treat but may respond to a combination of morphine, bronchodilators, and systemic corticosteroids.

Cough is usually treated with codeine when it is an isolated symptom. The opioids are cough suppressants but are best used only if the cough is causing distress—for example, disturbing sleep. There is probably little difference between the opioids in terms of their effectiveness as cough suppressants. Dextromethorphan 15-30 mg orally every four hours is as effective as codeine and has few side effects; codeine is very constipating. Methadone 5 mg two hours before retiring is a useful long acting drug for troublesome night time cough.

Steam inhalations help those whose cough is due to difficulty in expectorating sputum. Cough "mixtures" are best avoided; they often contain illogical drug mixtures—for example, an expectorant plus a cough suppressant. Traditional expectorants are ineffective. Bronchodilators may help cough by stimulating bronchial ciliary activity. Mucolytics—for example, bromhexine 8-16 mg orally every eight hours—reduce the viscosity of sputum. Unfortunately, most coughs in advanced cancer are due to irritant expanding mass lesions. In resistant cases prednisolone 10 mg orally is worth trying every eight hours.

CONSTIPATION

Constipation is common in the elderly, in patients who are bedridden or receiving inadequate diets, and in those taking a variety of drugs (opioids, anticholinergics, sedatives). Regular bowel motions should continue even if there is little dietary intake. An empty rectum does not exclude faecal impaction; if this is suspected the abdomen should be palpated and an abdominal radiograph ordered if there is still any doubt. It is astonishing how often bowel care is mismanaged.

Any patients who have cancer and who have been prescribed a regular opioid should always have a regular laxative started simultaneously. Usually a stool softener suffices. If, despite this, constipation ensues they should be instructed also to take as required a stimulant (senna) or osmotic (Milk of Magnesia) laxative. Bulk laxatives—for example, methylcellulose—are often poorly tolerated by patients who have cancer.

ITCH

Severe itch is very distressing and in advanced cancer is usually due to cholestasis. Good nursing care and topical treatment of the skin is vital, whatever the cause. Calamine lotion and menthol creams reduce itch by cooling the skin. Antihistamine and phenothiazines are only partly effective, largely because their antipruritic

effect is mediated through sedation. Hydroxyzine orally 25-50 mg every six hours is a useful agent.

Cholestyramine 4 mg every six hours is effective for itch caused by incomplete biliary obstruction, but gastrointestinal upset may occur, and it interferes with the absorption of some drugs and the fat soluble vitamins. Dosage should therefore be reduced once a therapeutic response occurs. The itch of lymphomas responds to effective treatment of the lymphoma or, failing that, to non-steroidal anti-inflammatory drugs. Antihistamine ointments are valuable in severe cases. Lignocaine gel applied topically may be tried in desperate cases.

DEPRESSION

Sadness and anxiety are common among patients who have advanced cancer. Severe depression is uncommon, and suicide is rare. About 40% of patients show some evidence of depressive illness. Non-somatic symptoms (particularly feelings of guilt and worthlessness) are helpful in diagnosing depression. Sympathetic support must be offered. Involvement of the family can be therapeutic. Morale is helped by relief of other symptoms and a good patient-doctor relationship. Unspoken fears—for example, about dying—should be gently inquired about.

If an antidepressant is required it is best to start with a low dose—for example, imipramine 12.5 mg at night—as side effects can be a problem. This is particularly true in patients already taking opioids. Whether the natural sadness of the terminally ill responds to drug treatment is unclear. Certainly it is usually eased by an understanding listener.

MALIGNANT BOWEL OBSTRUCTION

Malignant obstruction of the bowel is a common acute or subacute event in cancer of the colon or ovary. "Routine" nasogastric suction and intravenous fluids are unnecessary in patients who are unfit for surgery. Symptoms can often be managed with oral drugs, especially antiemetics and those that help to control pain from intestinal colic. Sometimes continuous subcutaneous infusion with a syringe driver containing an antiemetic (table II), an opioid for the pain, and an anticholinergic (for example, hyoscine) for the colic will control the symptoms. Faecal impaction must always be excluded.

Terminal phase

The final hours or days of life are indicated by fluctuating

TABLE II—Antiemetic drugs

Name	Preparations				Use subcutaneously in syringe driver	Dose (mg)/24 hours	Comments
	Tablet	Syrup	Injection	Suppository			
Prochlorperazine (Stemetil)	5 mg 25 mg	5 mg/5 ml	12.5 mg	25 mg (5 mg)	No (skin reaction)	15-50	Effective in many types of vomiting. Minimal sedation
Chlorpromazine (Largactil)	10 mg 25 mg 50 mg 100 mg	25 mg and 100 mg in 5 ml	25 mg 50 mg	100 mg	No (skin reaction)	50-150	As prochlorperazine but more sedating
Methotrimeprazine (Nozinan)	25 mg		25 mg		Yes (but some skin reaction)	50-150	Very potent antiemetic and analgesic. Considerable sedation
Haloperidol (Serenace)	1.5 mg 5 mg 10 mg 20 mg	10 mg/5 ml	5 mg 10 mg		Yes	5-20	Minimal sedation. Occasional extrapyramidal side effects
Cyclizine (Valoid)	50 mg		50 mg		Yes	150	Drug of choice in vestibular induced vomiting. Dry mouth
Metoclopramide (Maxolon)	10 mg	5 mg/5 ml	10 mg (100 mg)		Yes	30-60	Increases gastric emptying. Not sedative. Occasional extrapyramidal side effects
Dompriidone (Motilium)	10 mg	5 mg/5 ml		30 mg		30-60	Increases gastric emptying. Not sedative. No extrapyramidal side effects

Taken from: Baines M. *Drug control of common symptoms*. London: St Christopher's Hospice, 1986.

consciousness and increasing detachment from the surroundings. Agitation is not uncommon, and in those who are unconscious pain should be assumed to be the cause, and they should be treated by analgesic suppository or injections. A distended bladder or impacted rectum should be treated appropriately. If no cause can be found sedation with a phenothiazine can be used to avoid distressing relatives.

Few patients die dramatically, but it is wise to have morphine 10 mg and chlorpromazine 25 mg to hand in a syringe to be given quickly by a nurse (or competent relative if the patient is at home) should there be any dramatic distress or terminal event—for example, massive haemoptysis. Hyoscine 0.4 mg is a useful addition to help the “death rattle.” Most patients prefer to die at home, and their wishes should be respected whenever possible.

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The 18 authors cover the interests of all those associated with the care of terminally ill patients. The references are up to date, and the book is easy to read.

Conversations with Consultants

Dr G the neurologist

TONY SMITH

This is the sixth in a series of interviews with NHS consultants and academics; articles have appeared most weeks since 2 January. Dr G is a neurologist in a regional unit in the north of England.

For the most part I am as enthusiastic about clinical neurology as I was five years ago. Nothing that has happened in the health service has affected my clinical enthusiasm, but, like an increasing number of colleagues approaching the age of 60, I have begun to look at the prospect of retirement—and at the real possibility of retiring before the age of 65. After more than 25 years of clinical work as a consultant I find that the outpatient department has lost some of its charm and the challenge of the inpatients is also a little less stimulating. I believe this response is similar to that of the surgeon about to undertake his 300th gastrectomy, who almost certainly finds it somewhat mundane.

Yet in terms of morale concerning the clinical service and the facilities within this part of the health service I am as happy about things as ever I was. The role of the clinical neurologist has changed considerably with the advent of imaging. Those of us brought up in the era of the air encephalogram, ventriculogram, and angiogram acquired—through concentrated training—certain clinical skills. These have now been replaced by modern imaging techniques, and it has become almost fashionable to refer any problem of topographical localisation for a scan rather than rely on clinical skills to determine the nature and site of a particular lesion. This I might add is to the enormous benefit of the patient.

The hospital doctor who spends his career entirely as a clinician tends to take on a slightly different role as he approaches 60. One of my main functions now should be to pass on, in so far as is possible, clinical experience and other matters to do with medicine through

the ward rounds and formal teaching sessions but also informally. I see for myself an increasing responsibility not so much for the day to day care of patients (which of course does continue) but for the junior staff. Our junior doctors face worsening problems in their promotion, job opportunities, contracts, and terms of service. In many ways I see my most important task as supporting the juniors in their ambitions and trying to ensure that they succeed in their own aspirations. Many extremely well qualified and able registrars and senior registrars are currently frustrated, and it is the departmental head who must do his best to ease that frustration by giving them as much support as he can.

On looking back over the clinical years I realise that a consultant neurologist can choose very many compartments into which he can place his time. They include clinical work itself, investigational work leading to original writing, and opportunities to support clinical research, to review, and to spend time working for the various specialist journals. There is the responsibility to try to keep up to date with recent developments, private work, and teaching of both undergraduates and postgraduates. There is certainly enough available opportunity readily to fill every day.

Committee work

With an ever increasing demand for management within the health service most of my younger colleagues will be expected to undertake work as committee men, and if they find this interesting and fulfilling then no doubt they will be elected secretaries and chairmen of local committees and eventually undertake more work locally, regionally, and even nationally. If they aspire towards this work they should be encouraged to undertake it as early as possible in their careers. I was fortunate enough to be appointed to the various secretaryships and chairmanships of this and that committee at an early stage and was able to go through the local, regional, and, to some extent, national medical political scene in mid-career with an opportunity later of returning to full time clinical work before the age of 55. I feel in this respect it is important