Social services needed to have evidence of this trend away from placement in nursing homes over a reasonable period before reallocating funds. That stage is now approaching, and more money should be available soon for care in the community. Paul Meredith now wants to see the greatest possible flexibility in budgeting thus allowing more innovative approaches, and wants to pass decision making to the lowest operational level as quickly as possible. After all, a person's care plan should depend on their needs as identified by assessment, not on reaching targets for numbers of residential placements. Nevertheless, the Welsh Office's aim to reduce residential care is looking increasingly realistic.

Julie Mullins, associate director for commissioning at Gwent Health (the combined health authority and family health services authority), says that the first stage of the change has gone smoothly and confirms that overall it has not caused any problems of bed blocking.

In the six months from 1 April the average length of stay for elderly people in hospitals throughout the county fell by two days. Long standing good working relationships between hospital staff and social workers have made the transition easier. Julie Mullins recognises that within the broadly encouraging statistics there could be individual cases where there have been delays and difficulties. But she expects an even closer relationship with social services to develop, including the possibility of joint commissioning and contracting. This idea is also welcomed by Paul Meredith and

by Mrs Fiona Peel, chairman of the community trust, who feels that there has been a sea change in the attitude to the links between health and social services.

Conclusion

The safe conclusion is that it is too early to assess the impact of the community care reforms in Gwent. Nevertheless, some positive things can be said at this stage. There have been no disasters, despite a change in funding which evoked considerable fears. The general view is that it has been managed commendably smoothly. Most service providers believe that they have been delivering a better service since April that is more suited to the needs of the user. There is much more optimism than pessimism about the longer term consequences, as the shift of funds towards community care packages continues.

The data quoted about residential placements in Gwent suggest that this optimism is well grounded and that the attractive packages of community care intended by the reforms will soon be on offer more widely.

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Current Issues in Cancer

Cancer of the prostate

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This is the second in a series of articles examining developments in cancer and updating what we know about the disease

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Prostate cancer presents a growing health problem in Western societies as longevity increases. It is characteristically a disease of elderly men associated with the development of osteoblastic bone metastases and initial hormone responsiveness to androgen deprivation. Previously regarded as a Cinderella of cancers, there is currently more controversy concerning the detection and management of both localised and metastatic disease than for any other common malignancy. A balance needs to be drawn between the potential gains of more aggressive management and the disadvantages in terms of increased treatment side effects and cost, taking into account both the natural course of the disease and the life expectancy of patients.

In England and Wales in 1987 there were 10 837 new cases of prostate cancer. In 1991 prostate cancer ranked second to lung cancer in mortality from malignant disease in men, with 8570 prostate cancer deaths. This pattern of increasing incidence is common to other Western countries. In the United States prostate cancer is now the most frequently diagnosed male malignancy, with 132 000 cases per year¹ and a lifetime risk of 9-11% of developing the disease.²

Although prostate cancer predominantly affects the aging male population, it has been calculated that men dying of the disease lose on average nine years of life.³ In the United Kingdom morbidity and mortality from prostate cancer can be expected to rise as the longevity of the population increases. Currently some 50-60% of men present with metastatic disease,⁴ but as prostate

awareness and programmes of early detection become more widespread there will be an increasing incidence of patients diagnosed with early disease, as is happening in North America.

Epidemiology and aetiology

Worldwide there seems to be an increase in the incidence of and mortality from prostate cancer (table 1). Part of this increase may be due to improved diagnostic accuracy. The wide international variation, however, suggests that environmental factors are implicated in the aetiology and that a Western lifestyle leads to an increased risk. Necropsy studies show foci of microscopic well differentiated prostatic adenocarcinoma in 30-40% of men aged 75 or over.⁵ Inter-

TABLE 1—Age standardised prostate cancer mortality and incidence rates per 100 000 men aged 30-74 in various countries in 1985

Country	Mortality 1985	Recent 5 year trends†	Incidence 1985 (from selected regional cancer registries)	Recent 5 year trends†
United States:				
Black males	17.5	1.5	151.6	(3.1)
White males	—	—	88.5	12.6
England and Wales	15.2	7.2	32.9	14.1
Japan	3.3	8.4	10.1	30.2

†Recent trends: estimated mean percentage increase per five year period in age specific rates (30-74 years) over 15 years centred on 1980. Parentheses denote recent trends not significant at 5% level. (Adapted from Coleman *et al.*⁶)

estingly, this prevalence of "latent" cancer is very similar in different geographical populations⁶ despite the 10-fold variation in clinical incidence of carcinoma of the prostate. Possible risk factors for prostate cancer are listed in box 1. Most convincing are correlations with a high fat diet (positive) and a diet rich in yellow and green vegetables (inverse), which may act on the prostate through modification of circulating sex hormones⁷ and so lead to possible methods of primary prevention. Genetic factors may be implicated in the familial aggregation of cases.⁸

Box 1—Possible risk factors for prostate cancer

- *Diet*
 - High fat consumption
 - Low green vegetable consumption
- *Genetic*
 - Family history of prostate or breast cancer
- *Occupational*
 - Cadmium exposure³⁷
 - Radiation exposure³⁸
- *Sexual history*
 - Number of sexual partners³⁷
 - Frequency of intercourse³⁷
- *Medical history*
 - Vasectomy³⁹
 - Benign prostatic hypertrophy³⁷

Detection, diagnosis, and staging

Localised prostate cancer is most commonly diagnosed during investigation for obstructive urinary symptoms. Asymptomatic disease may be detected by digital rectal examination or by prostate specific antigen estimations. Metastatic disease most commonly presents with bone pain. Assessment and staging of local disease (box 2) is usually by digital rectal examination alone, but for patients considered for radical surgery transrectal ultrasonography or more recently magnetic resonance imaging can be considered. Neither of these, however, is reliable in

Box 2—Staging of primary prostate cancer

- T1—Clinical unapparent tumour, not palpable nor visible on imaging
- T2—Tumour confined within the prostate
- T3—Tumour extending through the prostate capsule
- T4—Tumour fixed or invading adjacent structures other than seminal vesicles

distinguishing between T2 and T3 disease.⁹ Transrectal ultrasound guided biopsy is increasingly becoming the diagnostic method preferred in patients who do not require transurethral resection. Both computed tomography and magnetic resonance imaging can identify significantly enlarged pelvic lymph nodes but underestimate the frequency of involvement, which varies from nil for focal well differentiated tumours to 18% for T1B/T2 cancers and 43% for T3 tumours when assessed by pelvic lymphadenectomy.¹⁰ Recent advances in laparoscopic surgery may permit more widespread and minimally invasive but still accurate lymph node staging.¹⁰

Bone scanning with relevant confirmatory radiology is the most appropriate method for detecting metastatic spread (fig 1). Prostate specific antigen estimation is valuable, as the degree of increase correlates with disease extent. Patients with prostate specific antigen concentrations <20 ng/l are very unlikely to have positive bone scans; conversely concentrations raised to 60 ng/l or more are strongly predictive of

FIG 1—Skeletal metastases detected by bone scanning in prostate cancer. Bone scanning is most sensitive method of detection. "Hot spots" may be present throughout axial skeleton

metastatic disease.¹¹ It must be remembered that raised concentrations may also occur in benign prostatic hypertrophy and prostate specific antigen density (which takes gland volume into account) gives better discrimination between benign and malignant disease.

Is there a case for early detection and screening?

The outcome of treatment for localised prostate cancer depends on the disease stage and histological grade, which correlates closely with the volume of disease. Tumours most commonly arise in the peripheral zone of the prostate, and early prostate cancer is usually asymptomatic. Symptoms of prostatism are usually associated with advanced localised disease, unless accompanied by additional benign prostatic hypertrophy. It is therefore reasonable to consider programmes for early detection or screening in order to find small cancers. However, for such a programme to have an effect on mortality the natural course of the disease must be such that it remains in a truly localised form when first detectable. Candidate tests for early detection include prostate specific antigen estimation, digital rectal examination, and transrectal ultrasonography with or without biopsy.¹² Effective treatments must be available for localised disease and the programme in general should be cost effective.

There have been concerns that because of the high prevalence of latent prostate cancer early detection programmes may uncover much disease which does not need to be treated. This is probably unrealistic, as

the three methods of investigation are not sensitive enough to detect tumours smaller than 0.5 cm.³ In addition, there is no proof that immediate radical treatment with prostatectomy or radiotherapy improves outcome when compared with a "watch and wait" approach for patients with early localised disease. Roughly 1.5-2.5% of men aged 50-70 would be found to have prostate cancer on a single screening evaluation,¹³ but as the specificity of the three tests is comparatively poor large numbers of ultrasound examinations and prostatic biopsies are required to detect these tumours. A balance must be drawn between the morbidity and anxiety caused by unnecessary investigation and the likely clinical benefit to those men found to have prostate cancer. What is required is a rigorously performed study including a control population to assess the magnitude of any benefit on prostate cancer mortality.

What is the optimal management of localised disease?

Localised prostate cancer usually progresses slowly, with an estimated doubling time of two years based on prostate specific antigen estimations.¹⁴ Reported results of series of patients treated with radiotherapy or surgery need to be placed in context with the natural course of the untreated disease. Clinical progression of well differentiated focal T1 tumours is unusual and deaths from carcinoma of the prostate are exceptional. Poorly differentiated T1 or T2 cancers progress with time and mortality from prostate cancer increases with the duration of follow up (table II). Tumour factors

TABLE II—Development of metastases and cancer related deaths from prostate cancer managed by a "watch and wait" policy

Tumour stage/grade	Metastases (%)		Cancer deaths (%)	
	5 years	10 years	5 years	10 years
T1 focal/grade 1	6	8	1	4
T1-T2/grade 2	16	42	3	13
T1-T2/grade 3	49	74	33	66

Data from Chodak *et al.*⁴⁵

which help predict the course of disease include histological grade, extent of glandular involvement for T1 disease, and DNA ploidy.^{12,15} However, patient factors are also important in determining the optimal approach. In a series of 120 patients (median age 74) with predominantly advanced localised disease tumour progression was recorded in 80% but only 20% died of carcinoma of the prostate compared with 60% from other causes. Cause specific survival at five years was 80%.¹⁶ Clearly radical local treatment could not have made a major impact on this patient population, but the situation could be very different for younger, fitter patients with longer life expectancy.

At present it seems reasonable to offer curative therapy to men judged to have a life expectancy of 10 years or more, though there is no compelling evidence that a close "watch and wait" policy with deferred treatment until the time of clinical progression would produce inferior results. The relative merits of radical radiotherapy and total prostatectomy depend both on local tumour control probability and on treatment morbidity. No adequate study has compared these treatment alternatives,^{17,18} and both are considered as standard management options for patients with disease confined to the prostate.

The probability of radical radiotherapy achieving clinical local control of prostate cancer depends on disease bulk, and control rates 10 years after treatment are around 95%, 80%, and 75% for patients with T1, T2, and T3 disease respectively. Corresponding overall 10 year survival rates are about 70%, 50%, and

40%,¹⁹⁻²² reflecting the higher incidence of metastases with increasing stage of disease. Though 70% of patients with T3 and T4 tumours develop metastatic disease within 10 years of treatment, radiotherapy is still valuable in this group, preventing symptomatic pelvic recurrence in most cases. Local failure itself, as well as tumour grade and T stage, predicts the development of metastatic disease.

Methods to improve the results of local treatment by radiotherapy are currently being developed. "Conformal" radiotherapy techniques using the latest imaging and beam shaping devices to deliver radiation more precisely may permit a safe increase in radiation dose.²³ The use of neoadjuvant luteinising hormone releasing hormone treatment²⁴ is undergoing an extensive prospective randomised study in the United States with promising preliminary results suggesting significant improvements in local control rates.²⁵ A Medical Research Council trial comparing radiotherapy with radiotherapy and orchidectomy or orchidectomy alone has shown that early androgen deprivation prolongs the time to development of metastases.²⁶

Prostatectomy is widely and increasingly practised in North America and continental Europe. It is as yet infrequently performed in Britain. Surgery is generally restricted to younger fit patients with T1 or T2 cancers and is preceded by pelvic lymph node dissection, diseased lymph nodes contraindicating further surgery. In general, patients treated by radical prostatectomy have enjoyed survival similar to that of an aged matched population.²⁷ In Belt and Schröder's series only 16% of patients had died of prostate cancer after 20 years of follow up,²⁸ and in a recent reported series of patients treated for T1 and T2 cancers 10 year survival was 90%. three quarters of patients remaining free of any recurrence.²⁹ Nerve sparing prostatectomy was first described in 1983.³⁰ In skilled hands urinary continence rates are over 95%, potency is preserved in about half of men (depending on patient selection), and local recurrence rates are low.³¹

There is clearly a need for a prospective randomised study to see how radical treatment affects the outcome of localised prostate cancer and to establish the relative merits of radiotherapy or surgery over a watch and wait policy. The Medical Research Council Prostate Sub-group plans to initiate such a study.

What is the optimal management of metastatic disease?

Prostate cancer is particularly characterised by osteoblastic bone metastases (fig 2), though spread to

FIG 2—Typical osteoblastic skeletal metastases in prostate cancer. Pathological fracture of femoral neck has been treated by internal fixation

Box 3—Treatment options to produce androgen deprivation in prostate cancer

- Orchidectomy
- Luteinising hormone releasing hormone
- Antiandrogens
 - Non-steroidal:*
 - Flutamide
 - Nilutamide
 - Casodex
 - Steroidal:*
 - Cyproterone acetate
- Oestrogens
- Complete androgen blockade

lung, liver, and soft tissue is increasingly evident as the disease progresses. Androgen deprivation has been the mainstay of treatment since the 1940s³² and produces some of the most dramatic and reliable responses in oncological practice. Roughly 80% of patients with metastatic disease have symptomatic benefit, with a median duration of response of 12-24 months and an overall median survival from the time of treatment of symptomatic metastases of about 2.5 years.

New methods of medical castration have given more acceptable alternatives to patients, and available options are listed in box 3. Pathways of androgen biosynthesis are shown in figure 3. Testicular androgen production is driven by release of luteinising hormone releasing hormone and of luteinising hormone from the hypothalamic pituitary axis. The active metabolite of testosterone is dihydrotestosterone, which binds to nuclear androgen receptor in normal and malignant prostate epithelial cells. Roughly 5% of circulating testosterone may come from the adrenals. After orchidectomy there is a rise in luteinising hormone releasing hormone and luteinising hormone concentrations, and side effects are those of loss of libido. Hot flushes may also be troublesome. The 1980s saw the development of luteinising hormone releasing hormone agonists (box 3) which are given by convenient once monthly subcutaneous depot injections.

Dihydrotestosterone + androgen receptor $\rightarrow$ Nucleus

FIG 3—Pathways of androgen biosynthesis. (Courtesy of Professor M Jarman)

Continuous stimulation of the pituitary by luteinising hormone releasing hormone agonists results in the inhibition of luteinising hormone secretion, and side effects of these agents are similar to those of orchidectomy. At the start of treatment there may be an initial rise of luteinising hormone secretion and therefore of testosterone concentrations. This can give rise to a "flare reaction," including increases of bone pain, spinal cord compression, or urinary obstruction. This effect may be blocked by giving an antiandrogen for several days before and for two weeks after the first depot luteinising hormone releasing hormone injection.

There are two classes of antiandrogen. The non-steroidal group (flutamide, nilutamide, and more recently casodex) is pure antiandrogens, which compete with androgens for binding sites at the androgen receptor in the nucleus of prostate cancer cells. Their use is associated with a rise in luteinising hormone and testosterone concentrations as the negative feedback of androgens on the pituitary is blocked. This secondary rise in circulating testosterone may reduce the efficacy of non-steroidal antiandrogens, and these agents are not routinely used as first line treatment. Side effects include gynaecomastia and gastrointestinal upset (particularly with flutamide), but libido may be maintained. Cyproterone acetate is a steroidal antiandrogen which has additional progestational effects which inhibit gonadotrophin secretion and so lowers testosterone to castrate concentrations. This dual action makes cyproterone acetate suitable as first line hormone therapy as an alternative to orchidectomy or luteinising hormone releasing hormone analogues. Side effects are those of androgen deprivation. Cardiovascular risks are substantially less than with oestrogens, but liver dysfunction and fatigue have been reported.

Oestrogens act mainly by a central mechanism blocking luteinising hormone releasing hormone secretion and reducing serum testosterone to castrate concentrations. They cause appreciable cardiovascular mortality and are no longer used as first line therapy.

There is currently considerable controversy about the significance of the small amounts of androgen produced from the adrenals. This has led to the concept of complete androgen blockade, which combines surgical or medical castration together with an antiandrogen to block the activity of any testosterone derived from the adrenals. The first prospective study to be reported from the National Cancer Institute suggests that there may be a small advantage for patients with good performance status and small volumes of disease.³³ A further 26 randomised studies of complete androgen blockade are in various states of completion. Some suggest that there may be benefit from the additional use of the antiandrogen flutamide, but meta-analysis will be required before definitive conclusions are made.³⁴ There is also debate about the most appropriate timing of hormone therapy in men with asymptomatic metastatic or advanced localised disease. The Medical Research Council should shortly complete a large randomised study to compare immediate and deferred androgen deprivation.

What options are available for hormone relapsed prostate cancer?

Progressive prostate cancer is characterised by general debility, anorexia, malaise, and most particularly bone pain. In contrast with the dramatic responses of initial hormone therapy, second line manoeuvres produce responses in at best 30% of patients, and these are usually of small degree and short duration. After orchidectomy or treatment with luteinising hormone releasing hormone agonists the addition of corticosteroids³⁵ acts by suppressing con-

centrations of adrenocorticotrophic hormone and adrenal production of androgens and is arguably as effective as more expensive alternatives using anti-androgen drugs. When luteinising hormone releasing hormone agonists have been used as first line treatment most clinicians continue with some form of androgen suppression, as progressive prostate cancer may still retain a degree of androgen sensitivity. Prostate specific antigen estimation is a useful monitor of any second line treatments that are introduced, and if no biochemical response is seen within a few weeks such methods should be abandoned.

Cytotoxic chemotherapy has a very limited role. Elderly patients with extensive bone marrow disease tolerate treatment poorly, and reported response rates are between 10% and 20% and of short duration. Experimental options include the use of high dose ketoconazole, which interferes with synthesis of testosterone precursors, and the anthelmintic suramin, which inhibits various growth factors, but the potential for neurotoxicity is high.

Radiotherapy in addition to the judicious use of appropriate analgesics remains the most valuable option for palliating bone pain. Around 80% of patients obtain substantial relief with a single treatment of 8 Gy, and in general this is to be preferred to longer fractionated courses.³⁶ For patients with multiple sites of metastasis (fig 1) and pain widefield or hemibody irradiation can be used. A recently evaluated alternative is to treat with strontium 89.^{40,41} Although expensive, this isotope gives effective relief in 70-80% of patients and compared with external beam techniques slows the onset of new sites of bony discomfort. The bisphosphonate group of drugs may also have a valuable role, as in breast cancer and myeloma, and their use is currently under investigation in Medical Research Council trials.

Conclusions

As the longevity of the population increases morbidity and mortality from prostate cancer will continue to rise. Strategies for disease prevention and early detection need to be developed and rigorously tested and we need to learn more about the relative merits of local treatment options and their impact on disease control and mortality. Studies are required to see if there is any benefit from adjuvant hormone therapy, which may now be more acceptable following the development of medical forms of androgen deprivation. In the near future the results of prospective randomised studies should give a clearer indication of the role of complete androgen blockade and of the optimal timing of hormone therapy in metastatic disease. But until fundamentally new treatment approaches are devised the palliation of hormone refractory disease will remain a major challenge to all concerned with the care of patients with prostate cancer.

I am at present coordinating a study at the Institute of Cancer Research in collaboration with the British Prostate Group to identify men with prostate cancer who have a family history of the disease or who develop prostate cancer at a young age (under 55) to examine possible modes of inheritance through genetic linkage analysis. Clinicians with patients in these categories can contact me for further information.

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