Current Practice

URINARY TRACT DISEASES

Cancer of the Prostate—II

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Management of Metastatic Disease

Apart from local spread, the disease becomes disseminated by the lymphatic and venous routes. Though pathological studies indicate that the former may be commoner and early, most symptoms are due to blood-borne deposits. Involvement of adjacent bones and particularly the lumbar vertebrae is explicable by the distribution of the venous channels draining the periprostatic venous plexus, while distal involvement of the skeleton and soft structures is due to tumour emboli. Local lymphatic spread often remains concealed for a long period owing to the fact that the regional lymph nodes are deeply placed in the pelvis but serious obstruction may ultimately ensue and cause oedema of the feet. Occasionally superficial lymph node involvement may occur as the result of retrograde spread of lymphatic embolism.

Though no structures are exempt, most of the clinical features of the metastatic disease are related to bone involvement. Among these, pain (due to the extension of secondary deposits and the reactive process which surrounds them) is the main symptom. Less frequently pressure on the nerve roots issuing from the spine or cranial foramina may lead to selective paraesthesia or paralysis. Diffuse replacement of the bone marrow may likewise interfere with haemopoiesis and cause severe anaemia. Hence supplementary general treatment may be required for these features.

By the time symptoms become apparent probably widespread dissemination has already occurred, and for this reason both surgery and radiotherapy will have little part to play except as strictly local palliatives or in relieving any urinary obstruction. Chief reliance must therefore be placed on endocrine control therapy; a response may be expected in about 80% cases and, though of uncertain duration, there can usually be little question of withholding treatment at this stage of the disease unless symptoms are minimal.

Endocrine Control Therapy

Probably the activity of prostatic cancer, even in the later stages of the disease, is often dependent to some extent on androgen stimulation. Endocrine control therapy therefore aims to suppress or eliminate the main sources of androgen production, thereby alleviating symptoms and retarding the progress of the disease. Possibly also some of the synthetic hormones employed exert a direct effect on the metabolism of the tumour cells. Nevertheless, there are no grounds at present for assuming that such treatment is ever curative, and indeed in many cases the response is short and in some, even

negligible. Despite this, however, treatment can achieve substantial symptomatic improvement and prolong survival in comfort.

It is convenient to consider endocrine control therapy in two stages.

Initial Treatment

The initial choice lies between oestrogen therapy and castration, either of which can cause comparable symptomatic relief.

Castration is a definitive procedure which acts by depriving the patient of his main depots of androgen production. Infertility is an inescapable sequel, but apart from this there are no side-effects except for a sense of genital inferiority—which can be offset by the performance of a *subcapsular* orchidectomy to give a better cosmetic result. This operation is particularly suited to patients who are unable to sustain treatment with oestrogens either through intolerance, mental incapacity, or medical contraindications. In other circumstances supplementary oestrogen therapy may also be given, and some statistical evidence suggests that a combination may extend the duration of the response in patients with widespread metastatic disease.

Oestrogen therapy aims at the general suppression of androgen production by the testes and possibly at the site of action. Conceivably also some of the synthetic preparations currently used may act directly on the tumour cells. Histological changes in the prostatic epithelium may be noted within forty-eight hours of starting treatment.

In addition to genital shrinkage and a decline in libido various side-effects may ensue. Though many of these are of a minor feminizing character—such as change of complexion, loss of facial hair, and swelling of the breasts—they may nevertheless prove obnoxious to a fastidious patient. Mammary enlargement can be prevented by a preliminary course of local x-ray therapy but this must be applied *before* starting treatment if it is to be effective.

Of more serious concern is that oestrogen administration inevitably leads to some measure of salt and water retention. In most cases this causes little disturbance beyond perhaps a slight "illusory" gain in weight but caution is required in patients with incipient cardiac failure. Diuretics to reduce the fluid load may possibly precipitate urinary difficulty if any significant obstruction remains at the primary site. The suggestion that oestrogen therapy predisposes to thrombosis has, as in the case of the pill, to be viewed in perspective and equated with the merits of such treatment. There is at present little indication that, in relation to age, any significant increase in mortality from this cause is likely, and if applied judiciously there can be no doubt that the benefits far outweigh the potential risks.

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Against this catalogue of side-effects must be placed the obvious advantages of ease of administration and the dramatic relief of symptoms which commonly ensues. Though relapse may occur ultimately, some cases appear to remain adequately controlled without ill effect throughout a normal lifespan.

The choice of oestrogen and the method of administration may have to be adjusted to the symptomatic needs as well as to tolerance and the mental capacity of the patient to sustain treatment. Orally-active oestrogens are available in natural or synthetic forms and both can be modified for parenteral use. In general synthetic hormones are preferred and probably none is more effective than stilboestrol, which remains the initial preparation of choice. Treatment should begin with 50 mg. b.d. (25 mg. tablets are available), reducing to half this amount as a maintenance dose after three months if symptoms are adequately controlled. This level, though possibly high by some standards, is probably more effective in postponing relapse and would appear no more likely to induce complications. Some patients, however, are unable to tolerate oral stilboestrol, even in small doses, on account of nausea and vomiting. In such event, if it is wished to avoid castration as an alternative, a natural hormone (e.g. Premarin) can be substituted or treatment given by parenteral route.

Intravenous therapy using soluble phosphorylated stilboestrol (Honvan) 250 mg. daily, either by intravenous drip or slow injection, may be valuable in controlling urgent symptoms for the interim relief of impending urinary obstruction, but the inconvenience of continued administration and the risk of hepatic damage renders this method unsuitable for prolonged use. Honvan tablets (100 mg. daily), however, may be prescribed orally instead of stilboestrol.

Intramuscular injections of phosphorylated oestradiol (Estradurin—80 mg. monthly) provide a method of depot therapy. Here the oestrogen component is of the *natural* variety, and possibly less effective, but good results have been achieved, particularly in cases with metastatic disease. The main drawbacks of depot therapy are that the absorption rate may be extremely variable and that when once the dose has been delivered it cannot readily be retrieved. Hence caution is thus required to avoid "water logging" in patients with cardiovascular disease.

Chlorotrianisene (T.A.C.E.) has been recommended from animal studies, which indicate that this substance may prevent compensatory adrenal hyperplasia (and hence the possibility of supplementary androgen production) known to follow castration. Clinical experience, however, casts some doubt on its efficacy as an oestrogen compared with stilboestrol, and the additional claim that mammary changes are less likely following its use perhaps supports this view. Currently, studies are proceeding to investigate the therapeutic possibility of reducing androgen production by blocking steroid metabolism in the adrenal cortex. Encouraging results in the treatment of metastatic mammary cancer have recently been reported, but it is not yet known whether these will apply to the prostate nor whether the substance employed is too toxic for general use.

Reports on the ability of progestogens to suppress prostatic cancer have so far been equivocal. Hence their use should be restricted to the treatment of relapsing cases when other conventional methods of endocrine therapy have failed.

Treatment of Relapsing Disease

Probably the most difficult problem in the management of prostatic cancer is relapsing metastatic disease when simple methods of endocrine suppression cease to be effective. Increasing pain, progressive anaemia, and episodes of urinary infection may all require treatment on general lines, which in

most cases can afford only temporary respite. By this time the malignant process will often have become autonomous, but in some cases an extended period of comfortable survival can be gained by endocrine surgery. The aim is to abolish the secretion of androgens or other hormones which may continue to influence the activity of the disease by deliberate ablation of their parent sources.

Adrenalectomy is seldom indicated in the case of the prostate, where the age of the patient and the gravity of the procedure—coupled with the uncertainty of the result and the need for substitution therapy—generally render it unacceptable. The same applies to surgical hypophysectomy. On the other hand the transnasal inoculation of radioactive material into the gland under radiological guidance may bring about functional suppression with resulting improvement. "Irradiation hypophysectomy" (see Figure), despite requiring a brief

Irradiation hypophysectomy. X ray of skull showing radioactive sources of yttrium⁹⁰ deposited in the pituitary by transnasal inoculation.

anaesthetic, is a relatively minor procedure well tolerated by patients even in the penultimate stages of the disease and at present probably affords the best prospect of relieving metastatic pain and prolonging survival in the advanced disease. A dramatic relief of symptoms can be expected in about half the patients so treated, and, though entailing the need for substitution therapy with cortisone, survival in comfort with restoration of ambulant activity over periods extending up to 3 years has been reported. Nevertheless, as in the case of other measures employed when the disease has become resistant to primary methods of endocrine control, the degree and duration of the further response at present remains unpredictable.

Further Reading

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