Current Practice

URINARY TRACT DISEASES

Cancer of the Prostate—I

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The prostate ranks high among the primary sites for cancer in the male and is indeed more commonly affected than any other organ in the genitourinary tract. Mortality statistics for England and Wales show an annual figure of about 3,900, an average of over ten per day, and when related to the population at risk suggest that one in every 1,700 men over 50 die with this condition each year. This seemingly alarming incidence is somewhat moderated by the knowledge that many cases occur in later life, when the impact of the disease is often less intense and the actual cause of death is more likely to be from intercurrent illness. Nevertheless, progressive morbidity is a common factor among those affected at an earlier age and if uncontrolled is likely to prejudice survival.

Presentation

Apart from the few asymptomatic cases brought to light by chance rectal examination, cancer of the prostate commonly presents in one of two ways. A majority—possibly four-fifths—begin with symptoms of urinary disability, generally indistinguishable from those of benign prostatic hypertrophy, while the remainder give little indication of involvement of the urinary tract and are first suspected on account of metastatic manifestations (bone pain, anaemia, etc.). Among the former a variable and (in treated cases) often extended interval may elapse before clinical evidence of secondary spread becomes apparent, while in the latter death may occur from widespread metastatic disease before the onset of any serious urinary disturbance. This apparently diverse behaviour possibly reflects an immunological variation in the tumour/host relationship.

Whereas in the metastatic disease there can be little question about the choice of suppressive endocrine therapy, the issue is rather more controversial in the case of lesions apparently restricted to the primary site. If local symptoms of urinary obstruction can be relieved by surgery or radiotherapy there may be some grounds for relying on an assumed natural immune defence mechanism and withholding endocrine treatment until further evidence of activity or dissemination occurs. On the other hand, it may be argued that oestrogen therapy is simple to give and that it may help to delay the onset of secondary spread. It is certainly well-suited to elderly patients, in whom minimal symptoms of urinary obstruction can often be effectively controlled, and to others who because of frailty or intercurrent illness are ineligible for other forms of treatment. At present there is a tendency to decry the use of oestrogens for treating the primary disease because of possible side-effects (including an alleged predisposition to thrombotic complications) and a belief that the average period of survival is not significantly extended. The evidence in favour of these views is by no means generally accepted and those who are old enough to recall the former relentless progress of the untreated disease are convinced that endocrine therapy can prove of inestimable benefit.

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Diagnosis

Since most cases present with urinary symptoms the first suspicion of the disease will commonly be aroused by rectal examination. Often the history does not distinguish benign and malignant prostatic disease and indeed, since both are apt to develop at the same age the two may even coexist. It may then be difficult to determine which is mainly responsible for the symptoms but local examination will generally decide the issue.

Typically the malignant focus arises in the periphery of the prostate and, giving rise to an indurated area which distorts the normal contours of the gland, becomes perceptible by the examining finger. Local spread occurs diffusely, both into the substance of the gland and, later, outwards into the region surrounding the seminal vesicles and the lower ends of the ureters. Extension around the rectum may likewise occur, though direct infiltration is rare.

Unfortunately in the initial and potentially curable stage of the disease the primary focus is so far removed from the urethra and bladder that it rarely gives rise to early symptoms. A few operable cases, however, may be discovered on account of urinary disturbance due to coexistent benign hypertrophy or as the result of fortuitous rectal examination. Nevertheless, not all indurated lesions of the prostate are malignant and even when a local nodule is confirmed by biopsy as carcinomatous there may be little or no indication of its activity or spread. In general most symptomatic prostatic cancers will have already extended beyond the scope of radical surgery, and the main issue will be to confirm the diagnosis and assess its extent before selecting palliative treatment.

Radiological Diagnosis and Scintiscanning

The chief importance of these methods lies in the demonstration of secondary spread. The radiological appearance of typical osteosclerotic deposits in the skeleton, when associated with palpable changes at the primary site (even in the absence of urinary symptoms), may generally be regarded as confirmatory. Occasionally a solitary osseous lesion may be difficult to distinguish from Paget's disease and biopsy may be called for. Likewise osteolytic metastases, though quite common, may be non-specific in indicating the primary site.

As in cancer of the breast early bone deposits may fail to show with conventional radiography; nevertheless, scintigraphy may reveal latent osseous involvement (Figs. 1a and b; Fig. 2), and studies with suitable isotopes would now seem obligatory in cases which might seem suitable for radical surgery. The demonstration of soft part metastases (Fig. 3) is non-specific for prostatic cancer and of little importance as a primary method of diagnosis since by the time they appear there will usually be ample evidence of widespread disease. Nevertheless, their subsequent behaviour may provide a valuable indication not only of activity but of the efficacy of treatment (Fig. 4).

Laboratory Studies

Estimation of the serum acid phosphatase remains the only specific laboratory test for prostatic cancer. The test relies on the capacity of adult prostatic epithelium to secrete the enzyme and on the fact that most prostatic cancer cells retain this function. Unfortunately, the serum enzyme level is seldom raised before the primary disease is well-established or metastasis has occurred, and hence the investigation is mainly confirmatory. Nevertheless, it may provide a rough index of the extent of the disease and of the response to treatment. Misleading values are sometimes obtained after vigorous rectal examination or even after an enema and the test should be deferred for at least 24 hours after either of these procedures. Haemolysis in the blood sample may likewise lead to a false-positive result owing to the liberation of acid phosphatase from the red blood cells.

Non-specific laboratory investigations include the erythrocyte sedimentation rate, haemoglobin estimation, and tests of renal function. None is of any particular diagnostic value but may help in a general evaluation.

Cytology and Biopsy

Examination of the prostatic fluid (expressed by rectal massage) for malignant cells requires skilled cytological

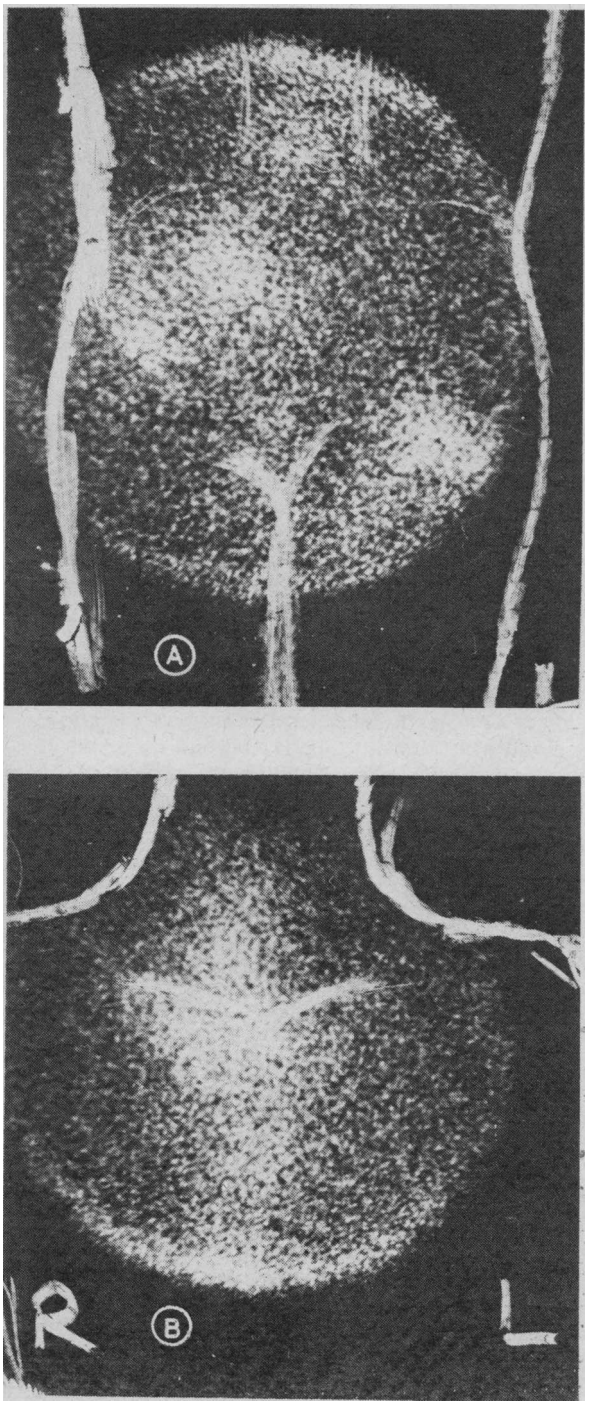

FIG. 1.—Scintigram (using Sr^{87}) showing concentration of the isotope (indicative of metastatic deposits) (a) in the lumbar spine, right ilium, and left ischium, and (b) at inner end of right clavicle (subsequently confirmed by biopsy).

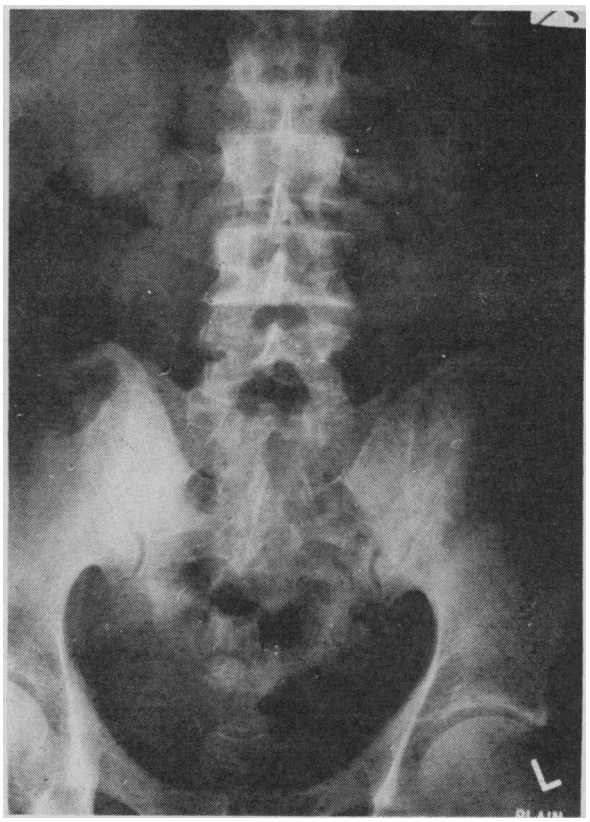

FIG. 2.—Radiological appearance of lumbar spine and pelvis in the same patient. The clavicular lesion could not be demonstrated radiologically.

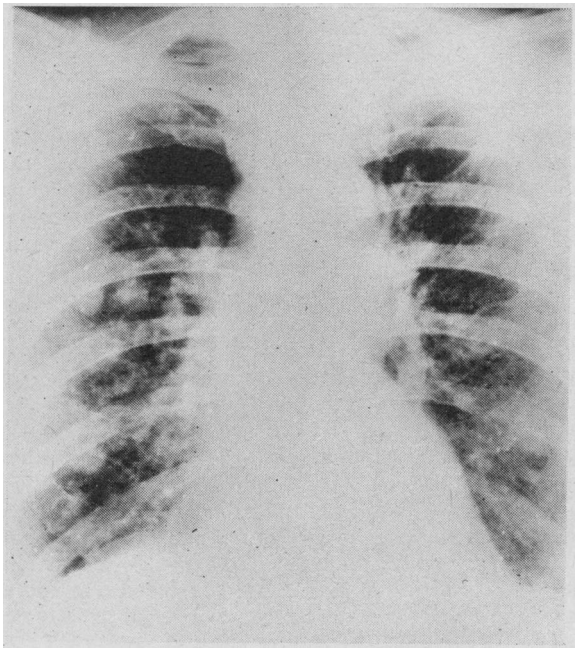

FIG. 3.—*X*-ray of chest showing well-defined metastatic deposits in the lung fields.

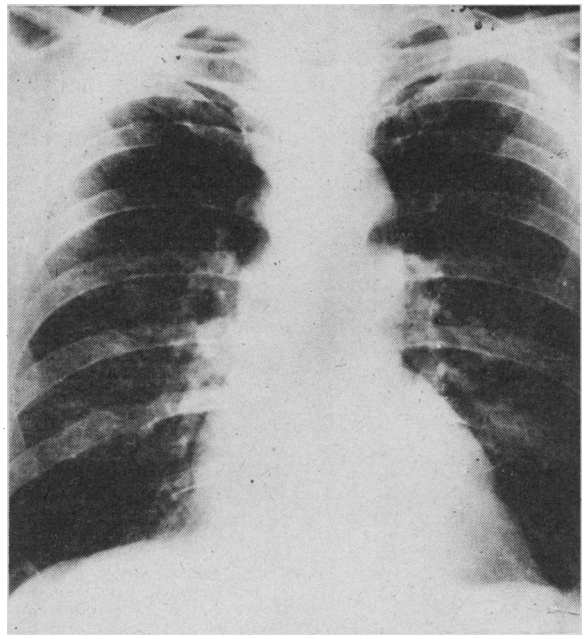

FIG. 4.—The same patient after treatment with stilboestrol for three weeks showing disappearance of deposits.

interpretation. Though often positive in well-established cases, the method is less reliable in the early stages of the disease and hence has little importance in routine screening. Biopsy is greatly to be preferred and will generally provide more adequate material with scarcely any greater risk or inconvenience to the patient. Until recently most methods of biopsy examination—whether by the perurethral, perineal, or rectal routes—were relatively crude and often unsuccessful in obtaining representative tissue. With the introduction of fine-needle transrectal aspiration biopsy using the modified Franzen needle (Fig. 5) these objections have been largely removed. No anaesthetic is required (beyond the local use of xylocaine gel) and after digital palpation of the suspicious area in the prostate, the flexible needle is advanced along a cannula attached to the examining finger and a suitable sample of tissue obtained by aspiration. Ejection of the tissue on to a glass slide enables a smear to be made which serves as a histological preparation.

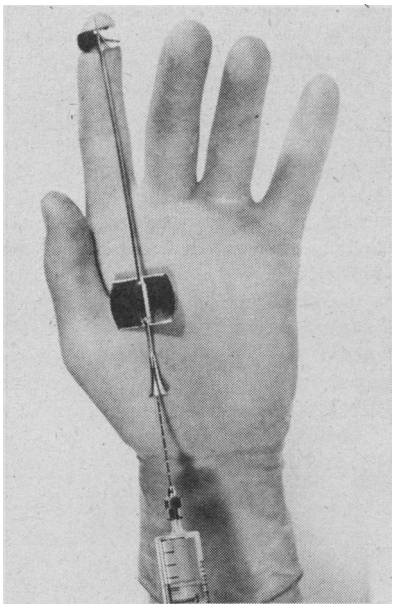

FIG. 5.—The modified Franzen needle used for transrectal aspiration biopsy.

This method is open to the criticism, common to all forms of biopsy, that it provides little or no indication of the activity of the disease. It is now well established that many men over the age of 60 harbour small latent foci of histological cancer in the prostate and that many of these never become overt. A positive finding must therefore be interpreted with caution and viewed in full clinical perspective.

Management

Methods of diagnosis have been emphasized since probably treatment is often misapplied either on the basis of an unconfirmed clinical suspicion or in relation to the stage of the disease. Most conventional therapeutic measures carry certain disadvantages and hence they must be used only with due regard to their hazards, as well as the benefits. The aim should therefore be to assess the apparent intensity and extent of the malignant process and to draw up a rational plan of management. The latter may have to be modified on account of age, intolerance, or lack of availability of certain forms of treatment, and the presence of intercurrent disease.

It is particularly important that all patients with urinary symptoms should first be subjected to full urological assessment. Irrespective of any symptomatic benefit from blindly applied conservative treatment the latent risks of urinary obstruction and infection should not be overlooked. In some cases some benign hypertrophy may coexist; since this is unlikely to respond to endocrine therapy, it is essential that the local condition should be properly evaluated.

Treatment of Primary Disease

Radical prostatectomy can play only a very small part in the treatment of prostatic cancer, and its range is limited to early lesions found on casual examination or in association with benign hypertrophy. Even in these there may be doubt as to the activity and the true extent of the lesion, and a conservative approach may be wiser. This view, though controversial, is influenced by the results of a survey in which a large unselected group of men were found to show more asymptomatic foci of prostatic cancer than could possibly be equated with the current death rate from the disease. Moreover, even in the best hands total prostatovesiculectomy carries a significant morbidity rate in terms of urinary incontinence, while—particularly in the elderly—alternative methods of treatment can nowadays often achieve a reasonable period of survival in comfort without resort to major operations. In the vast majority of cases by the time symptoms have drawn attention to the primary focus only palliative treatment is practicable. This is a commonplace situation since the initial signs of urinary obstruction are frequently ascribed to advancing age and casually disregarded until the disease is already well established. The issue then to be decided is how far the condition can be sufficiently relieved solely by measures directed towards the suppression or control of the malignant process and to what extent local surgery may be required.

Until recently the only effective means of diminishing the activity of the disease consisted of endocrine control therapy. Nevertheless, improved methods of supervoltage radiotherapy have now overcome many of the disadvantages of earlier techniques and are an acceptable alternative for local treatment. Even so, expert urological advice should be sought to confirm the diagnosis and assess the general status of the urinary tract before treatment is begun. In grosser degrees of obstruction when the patient first presents with complete (or near) urinary retention, it is less likely that such methods alone will succeed and adjuvant surgery may be called for. In its simplest form the latter consists of catheterization, which gives both immediate relief and time for investigation. Once the diagnosis is confirmed intensive therapy with oestrogens (preferably intravenously) or radiotherapy may sometimes relieve the obstruc-

tion to restore a semblance of normal micturition. In most cases, however, further surgery in the form of perurethral prostatic resection will also be needed and, in rare cases where benign hypertrophy predominates, formal prostatectomy may be necessary. The main danger in such cases stems from urinary obstruction rather than the cancer locally, and every effort should be made to avoid permanent suprapubic or catheter drainage.

Once the obstruction has been relieved it must then be decided whether continued suppressive therapy is called for. Where the initial disturbance has been minor, and metastatic activity is little, further treatment may be withheld until the onset of renewed symptoms. The response to endocrine therapy is often impermanent and at present the long-term results of radiotherapy remain unpredictable. On the other hand, if urinary symptoms or other signs of activity continue there may be little option but to resort to such measures immediately, either individually or in combination. In younger men (under 65) especially, the activity of the disease is likely to be greater and early energetic treatment may be indicated.

(This article will be concluded next week.)

TODAY'S DRUGS

L-Dopa—I

With the help of expert contributors we print in this section notes on drugs in current use.

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Over the last decade developments in pharmacology, biochemistry, and neurophysiology have culminated in a major therapeutic advance in neurology: the introduction of L-dopa for the treatment of Parkinsonism. Though this drug does not suit all patients, worthwhile alleviation of symptoms can be achieved in many cases and in some the beneficial results far exceed those of any previous form of therapy. These developments have been reviewed in detail,[1-3] and the following account summarizes the pharmacological background and present therapeutic status of L-dopa in Parkinsonism.

Pharmacological Background

Ever since Charcot introduced belladonna alkaloids (atropine and hyoscine) for the treatment of Parkinsonism these drugs have been the basis of conventional medical treatment. Their pharmacological action is blockade of the synaptic neurotransmitter acetylcholine. Twenty years ago the belladonna alkaloids were replaced by synthetic cholinergic-blocking drugs such as benzhexol (trihexyphenidyl), which were considered to be more effective in Parkinsonism.

The major development over the last decade has been the accumulation of evidence that dopamine, the precursor of noradrenaline, is a synaptic neurotransmitter in the corpus striatium and that the basal ganglia of patients with Parkinsonism are grossly depleted of this substance.[4] The therapeutic implications of this discovery were pursued by W. Birkmayer and O. Hornykiewicz[5] and A. Barbeau.[6] Attempts were made to replenish brain dopamine by giving patients its immediate precursor, L-3,4-dihydroxyphenylalanine (L-dopa, laevodopa), because dopamine itself does not readily cross the blood-brain barrier.

The results of these studies were encouraging, and a hypothesis emerged that acetylcholine and dopamine act as antagonistic transmitters in the central nervous system, just as acetylcholine and noradrenaline have opposing actions in the peripheral autonomic nervous system. Normally there is a balance between acetylcholine and dopamine but in Parkinsonism the latter's function is impaired and this results in cholinergic dominance. This situation may be corrected by either reducing cholinergic activity—as in traditional therapy with belladonna alkaloids—or by enhancing dopaminergic function—by administering L-dopa. Either form of treatment would be expected to restore the balance between acetylcholine and dopamine and a combination of both approaches might achieve a synergistic effect.

Therapeutic Actions

Early experience with low doses of L-dopa, often administered intravenously, led to conflicting though on the whole encouraging results. In 1967 G. C. Cotzias and his colleagues[7] reported that very large oral doses could be tolerated if the intake was built up gradually over a long period. With prolonged administration of high doses some patients experienced very impressive benefit. DL-dopa was used because it was cheaper than the separated L-isomer. Subsequent studies[8-13] confirmed these results and provided evidence that pure L-dopa was less toxic than the racemic DL-dopa.

Clinical reports of prolonged treatment of Parkinsonism with maximum tolerated doses of L-dopa now include experience of over 1,000 patients, many of whom have been treated in double blind therapeutic trials. A substantial proportion of patients derive very considerable benefit from this treatment. Precise figures vary from one series to another, but at a conservative estimate about 30% of an average population of Parkinsonian patients obtain an impressive therapeutic response. In a further 30% worthwhile improvement is achieved, and in the remainder the results are less satisfactory and are often dominated by prominent adverse effects.

The major clinical feature of Parkinsonism to improve during L-dopa therapy is hypokinesia—difficulty in initiating movement and a general loss of dexterity. Hypokinesia is the most disabling single component of the Parkinsonian syndrome, being responsible for the general deterioration in motor performance which leads to loss of working capacity and loss of independence. The improvement in hypokinesia induced by L-dopa is shown by increased facility in walking, greater range of facial expression, enhanced control of fine finger movements, less dysphagia, and reduced dysarthria.

Parkinsonian rigidity is also alleviated by L-dopa and in many cases tremor is decreased. Nevertheless, the latter is usually the last clinical feature to benefit and improvement may take several weeks. Posture, balance, drooling saliva, and oculogyric crises may be helped by treatment.

Parkinsonism is a complex syndrome of neurological deficits and the ultimate value of any treatment must be assessed by how far patients return to an independent active life and their relatives are relieved of nursing responsibility. Judged by these criteria the introduction of L-dopa represents a therapeutic advance of major importance in an area where treatment had hitherto been unrewarding. Idiopathic, post-encephalitic, drug-induced (for example, by phenothiazines or reserpine), and toxic (such as manganese intoxication) Parkinsonism have all been claimed to respond to L-dopa. Experience is at present too limited to decide whether the progressive course of idiopathic Parkinsonism is modified by treatment.

Selection of Patients

Precise prediction of therapeutic results is impossible, so all Parkinsonian patients should be offered L-dopa unless there is