Section of Urology

President J D Fergusson MD FRCS

Meeting October 25 1962

Some Aspects of the Conservative Management of Prostatic Cancer [*Abridged*]

by J D Fergusson MD FRCS
(*Institute of Urology, London*)

During the present century the general life expectancy of the population has increased. Greater importance is, therefore, now attached to the study and alleviation of the diseases of old age. In this respect cancer of the prostate provides a fertile field as its incidence rises steadily in later life to reach a clinical peak in the eighth decade (Table 1).

Table 1
Age distribution in 467 cases of prostatic cancer

Age in years	35–	40–	45–	50–	55–	60–	65–	70–	75–	80–	85–	90–94
No. of cases	1	1	2	15	28	63	96	105	90	42	17	3

Age unknown in 4 cases

At times, the activity of the disease may be so slight as to render it compatible with a relatively normal existence – at least among the less fastidious. The conception of 'living in symbiosis with cancer' is therefore one which can seriously be entertained in certain cases and may equally provide a worthy objective in the treatment of others. This is the theme which I shall seek to elaborate by drawing on a personal experience of upwards of 500 cases treated by conservative methods. Before doing so, however, it is important to view the disease in its full perspective and to draw attention to certain features which may affect its management.

Reference to recent cancer statistics shows that prostatic cancer occupies a high position in relation to malignant disease at other sites and, indeed, occurs with greater frequency than the combined incidence of all other neoplasms affecting the genito-urinary tract.

President's Address

Age

Those forms of malignancy which occur mainly in later life often arouse less sympathy than their younger counterparts. This is an age when the patient is normally expected to decline and overzealous treatment is often best avoided. Some of the more elderly patients fall into this category and the significance of the disease may thus be correspondingly reduced.

Activity

Prostatic cancer exhibits a wide spectrum of activity which can be extended at its invisible end to embrace the latent forms of the disease. In the clinical range, activity seems often to be governed by endocrine stimulation and this may partly account for its variable behaviour.

The relationship of the latent and symptomatic forms of the disease remains obscure, but the fact that both increase in frequency as age advances suggests that there may be some association. Nevertheless, the suggestion that hidden cancer is present in a high proportion of elderly men merits the consolation that from clinical evidence only a small proportion of such tumours ever become fully active. There is some reason, however, for believing that low-grade subclinical activity is not uncommon and Franks (1954), in a series of 69 cases of unsuspected prostatic cancer found at autopsy, noted infiltration of the gland capsule in over 75%. Similarly there are grounds for extending the conception of latency to apply also to the metastatic disease. Silent secondary deposits are not unusual and Clifton and his associates (1952) detected malignant tumour emboli in the sternal marrow in one-third of a group of patients otherwise deemed suitable for radical prostatectomy.

Practical Considerations

It is widely agreed that prostatic cancer generally commences at the periphery of the gland and the early 'operable' stage is usually obscured by its concealed position and lack of symptoms. Symptoms, in fact, *can* only develop as the result of

local or metastatic extension, unless they happen to arise coincidentally from other causes. The prospect of radical surgery is thus mainly restricted to a few cases in which a localized tumour is fortuitously detected either on routine health examination or during the investigation of some other disease. Even in such cases the potential activity of the disease may remain doubtful. Whether, in order to swell the number, one should encourage prophylactic rectal examination in middle age raises social and ethical problems with which we are not immediately concerned. At present, therefore, it must be accepted that most cases will continue to be first seen only when the disease has progressed beyond the limits of radical operability.

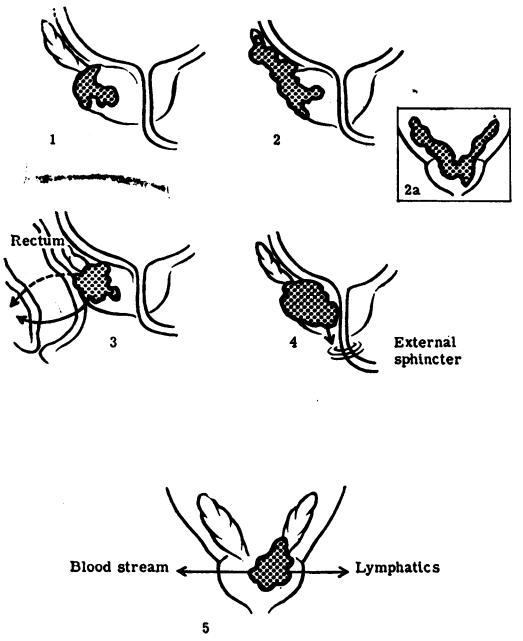

Fig 1 *The spread of prostatic cancer. 1–4, local spread. 5, metastasis*

Reference to the spread of the condition will show how symptoms arise and explain the usual modes of clinical presentation. Fig 1 shows some of the pathways of local extension: (1) Invasion of the gland substance; (2) infiltration of the capsule with spread to the vesicles and occasionally the ureter (the 'cabeza de toro' or 'bull's head' of the Spanish writers, 2a); (3) perirectal involvement with, rarely, penetration of the rectum; and (4) in advanced cases spread to the urinary sphincter. Early metastatic extension (5) is common especially via the lymphatics, but spread of this type is often silent. A majority of metastatic symptoms in fact arise from blood-borne deposits in the bones and other structures.

Presenting Symptoms

The symptoms fall into two groups corresponding with the development of the tumour at the primary and certain metastatic sites. It is remarkable how often one type will prevail and sometimes lead to the adoption of limited therapeutic measures when our true aim should be to treat the whole disease.

Reference to the literature reveals certain differences in the mode of presentation of the disease, according to whether cases are derived solely from urological departments or from the practice of a general hospital. The present series stems from both sources and relates to 467 cases personally seen and treated at St Paul's and the Central Middlesex Hospitals (Table 2). It is notable perhaps for showing a relatively high proportion in which metastatic symptoms *alone* provided the first indication of the disease; and also for the inclusion of 26 patients who had no symptoms referable to the condition at all. The latter were all patients who had attended for such reasons as inguinal hernia, rectal bleeding and so on, and in whom the prostatic lesion was discovered purely incidentally. It must be added, however, that all the tumours casually detected in this manner were already beyond the range of radical surgery.

Table 2
Mode of presentation in 467 cases

	No. of cases
Local symptoms only	363
Metastatic manifestations only	61
Combined local and metastatic symptoms	17
No symptoms directly referable to the disease	26

As might be expected, a majority of patients complained of symptoms related to the primary tumour. Comparatively few patients had simultaneous metastatic symptoms at the outset though secondary lesions, in fact, were often present. The urinary symptoms closely resembled those usually associated with benign prostatic hypertrophy and indeed showed few practical points of distinction (Table 3). It may be mentioned, however, that nocturnal incontinence (associated with residual urine) seems to be relatively more common in

Table 3
Initial local (urinary) symptoms in 380 cases (often in combination)

	No. of cases
Frequency	220
Difficult micturition	174
Retention	75
Painful micturition	42
Hæmaturia	40
Incontinence	22

malignant cases. It has also been suggested that hæmospermia is more likely when the vesicles are involved, but no examples were encountered in the present series. Among less common early features were intestinal obstruction due to silent perirectal infiltration and, in one case, a painful hæmorrhoid which proved to be the extension of a concealed primary tumour.

The remaining cases presenting with metastatic symptoms *alone* are remarkable not only for their number but also for the diversity of their complaints. Although the latter mainly consisted of pain referable to bony deposits there were several initial features of a more unusual type.

Some patients had themselves detected the presence of abdominal masses and enlarged superficial glands due to lymphatic involvement, while others had noted œdema of the leg from a similar cause. A few presented with neurological manifestations such as diplopia and facial palsy and (in one case) herpes zoster, resulting from involvement of the appropriate nerves.

I have deliberately spent some time in reviewing the initial symptoms, not only to emphasize their protean nature but mainly to provide an ample picture of the condition which we are called upon to treat.

In choosing the title for this Address I had in mind two objects, first the exclusion of the controversial matter of 'radical surgery' and, secondly, the opportunity for discussing the *humane* management of the disease. Let me now stress that conservative management commences at the first attendance of the patient. The initial examination and subsequent steps to confirm the diagnosis should thus be arranged to avoid undue discomfort and risk. Fortunately we have at our disposal several methods of investigation and a little thought as to their application may well prove in the best interests of the patient.

Diagnosis

In most cases the first suspicion of the disease comes about through rectal examination, and 371 of the 467 patients under review exhibited induration of the gland at the outset. This feature, however, was not appreciable in the remaining 96 despite the existence in many of urinary symptoms; 69 of the latter were, in fact, provisionally regarded as suffering from benign hypertrophy until further investigation disclosed the presence of cancer. It is important, therefore, to envisage the possible coexistence of benign and malignant lesions as this may well affect subsequent treatment.

Many advanced cases with urinary symptoms are unmistakable on rectal examination and the facility for detecting others doubtless increases with experience. Nevertheless there are probably few urologists to-day who are entirely confident of their clinical ability in this respect.

Hazards of presumptive rectal diagnosis: Fig 2 illustrates a case which presented with a hard nodule in the prostate having all the usual

Fig 2 *X-ray of case presenting with local induration of the prostate showing a bullet which had remained lodged in the gland for over forty years*

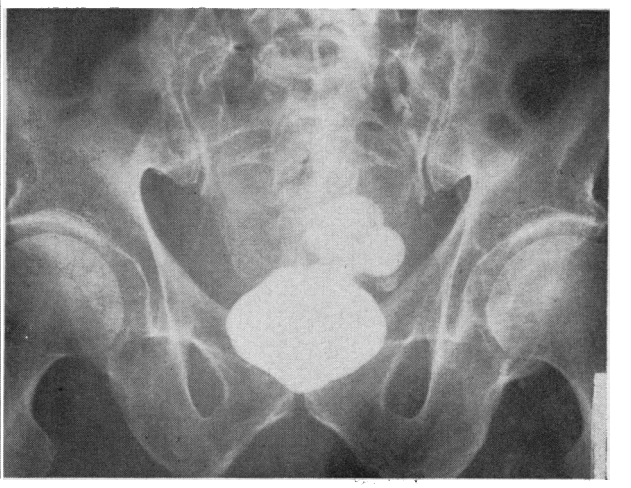

Fig 3 *Plain X-ray showing massive calcification of the prostate*

characteristics of localized malignancy. X-ray examination revealed a bullet which had remained lodged in the gland since the First World War! There are likewise many commoner causes of confusion such as chronic inflammation, prostatic calculi and even bilharzia. Fig 3 shows a case in which the prostate is completely calcified. Because of this and since even *conservative* treatment involves certain hazards it is important that the diagnosis should be fully confirmed before commencing treatment.

While ultimate proof rests with histology there are certain investigations which may aid in establishing the diagnosis without the need for obtaining actual tissue. Among these, X-ray examination, biochemical investigation and, to a lesser extent, cytological study of the prostatic fluid have come into conventional use. All have the merit of causing little disturbance to the patient and may often clinch the issue.

Fig 4 shows an example of positive radiological diagnosis in a patient who admitted to no urinary symptoms.

Biochemical investigation: Various methods have been suggested relating to what is known of the specific functions of the prostate. Of these, only estimation of the serum acid phosphatase has so far emerged with credit and unless carefully applied its value may be dubious. Raised levels were frequently encountered in the series but often only after the diagnosis had been otherwise assured. Nevertheless the introduction of the tartrate method and the use of specific substrates now gives promise of greater accuracy in the detection of early cases.

Cytological diagnosis is a method which commends itself mainly as a comfortable alternative to biopsy. Although open to the objection that massage of the gland may disseminate cancer cells, this risk is probably no greater than in actual biopsy, and I have never seen any disastrous consequences. The main drawback is that the prostate often tends to dry up in old age and it is sometimes impossible to express any fluid. Success, however, will often follow a preliminary course of stilbœstrol, and some years ago Gibson and I, with the expert assistance of Dr J Bamforth, were able to demonstrate the potential accuracy of the method (Fergusson & Gibson 1956).

Prostatic biopsy has perhaps been somewhat extravagantly used in the present series, mainly because at the outset it was decided that all cases should be histologically confirmed before qualifying for treatment. In recent years, however, this standard has been relaxed when other diagnostic findings were deemed sufficient. Nevertheless there is still scope for its employment and it can often usefully be combined with perurethral resection when serious urinary obstruction demands relief. Likewise sternal puncture and biopsy of secondary lesions may continue to have application when the primary lesion remains obscure. The point I wish to make, however, is

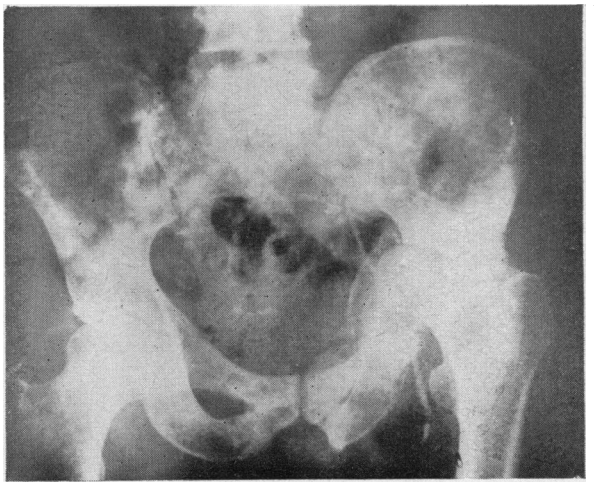

Fig 4 *Extensive secondary deposits in the pelvis with protrusio acetabuli and pathological fracture of the femoral neck in a case of prostatic cancer without urinary symptoms*

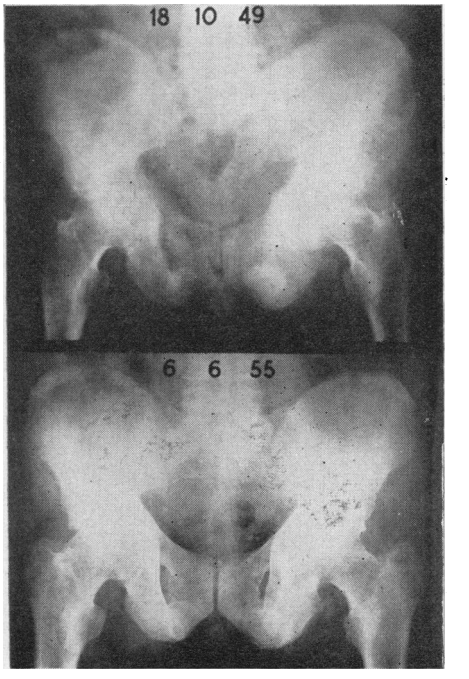

Fig 5 *X-rays of the pelvis showing control of secondary deposits in a patient receiving œstrogen therapy for over six years*

that the histology of the tumour contributes little to the subsequent choice of conservative treatment and can often well be omitted when the diagnosis is otherwise assured.

Table 4
Confirmatory diagnosis in 467 cases

		No. of cases
Radiological metastases		122
Raised serum acid phosphatase		200
Positive histology (or cytology):		
Prostatic biopsy	241	
Lymph gland biopsy	11	
Bone biopsy	6	366
Cytology (prostatic smear)	52	
Subsequent autopsy	56	

All cases in the present series were confirmed by a suitable combination of the foregoing methods (Table 4). The proportion with histological proof is notably high – largely for the reasons already given. Among these cases were some patients with prostatic obstruction who were submitted to perurethral resection/biopsy to investigate the response to stilbœstrol (Fergusson & Pagel 1945, Fergusson & Franks 1953), while others were examined to study the uptake of tracer elements and labelled œstrogens (Fergusson 1961). The remainder have qualified for inclusion on the basis of positive radiological, biochemical and cytological findings in support of the clinical evidence.

The object in compiling the series was to explore the scope of endocrine therapy and it is with certain practical aspects of this form of management that I shall now be finally concerned. It is my view that, at the present time, such treatment, combined where necessary with palliative surgery, continues to offer the best prospect of controlling the disease in a majority of cases.

Treatment

All forms of endocrine-control therapy, irrespective of whether hormones are administered or taken away, carry certain risks and inconveniences. Before instituting such treatment, therefore, it is necessary to be convinced of its potential value. I emphasize this because, after the initial wave of enthusiasm twenty years ago, opinion has been modified by the knowledge that some tumours (possibly upwards of 20%) are resistant, while others tend to relapse. Nevertheless there is ample clinical evidence to suggest that a majority show a favourable response although it is often difficult to translate this in an objective manner.

Some years ago I demonstrated the reaction of the primary tumour in a series of consecutive biopsies during the course of treatment with œstrogens (Fergusson 1946). Similarly, the response of secondary deposits has been gauged by repeated estimation of the serum phosphatase or by X-ray examination. Fig 5 shows the radiological appearances in a case followed over six years. Such comparisons, however, relate to individual cases and more comprehensive guidance as to the effect of therapy can only be obtained from studies of the survival of large groups of treated and untreated cases. Reference to the present series of 467 patients shows that 376 cases have now qualified for three-year follow up (Fig 6). Of these 319 received hormone therapy while 57 did not. The overall effect of endocrine control is obvious and the better survival of the treated cases closely agrees with the results in other large collective series. The relatively high initial mortality derives partly from the inevitable inclusion of advanced or resistant cases, but may also possibly be influenced by inadequate treatment.

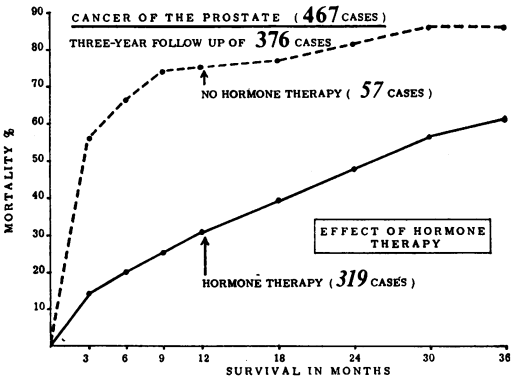

Fig 6 *Effect of hormone therapy; three-year follow up*

In the planning of specific treatment the conception of hormonal 'give and take' at present offers a choice (or combination) of œstrogen therapy and castration, the administration of steroids or adrenalectomy and, finally, pituitary suppression or ablation. The main problems are which methods to select, how and when to apply them, and the relative risks involved. General opinion favours initial treatment either by castration or the administration of female hormones. The mechanism of the latter remains obscure since, although it is widely supposed that many tumours are androgen dependent, the effect is possibly not merely a matter of hormonal antagonism. There is thus scope for a combination of the two and indeed this has been recommended in metastatic cases (Nesbit & Baum 1950). Nevertheless our own findings suggest that œstrogens, when given in sufficient dosage, induce

a response comparable to that of castration, and because of this a small but unpalatable operation can often be avoided. Orchidectomy has therefore been mainly reserved for cases where it was doubtful if the patient would continue taking œstrogens or where serious intolerance or dangerous side-effects ensued. It is useless when the testes have already been rendered atrophic by œstrogens. A preference for œstrogens may also be influenced by factors such as age and the sentimental value attached to the gonads.

Table 5
Œstrogen therapy for prostatic cancer (some œstrogens and their mode of administration)

	Administration			
			Depot therapy	
Class of œstrogen	*Oral*	*Intravenous*	*Subcutaneous*	*Intramuscular*
Natural	Ethinyl-œstradiol Premarin	—	Œstradiol	Estradurin
Synthetic	Stilbœstrol Hexœstrol Dienœstrol TACE	Honvan	Stilbœstrol	—

With regard to the choice of œstrogens this is nowadays almost unlimited, but reliance should be placed on preparations of proven value. These fall into two main groups (Table 5) – those derived from natural sources (such as pregnant mares' urine) and those synthesized on an entirely different chemical pattern. The former are somewhat more expensive and often less active by mouth in the doses customarily used. By comparison the synthetic œstrogens have a high oral potency and their chemical structure brings them into line with other cancerocidal substances which possibly augments their effect.

While oral administration is generally preferred there may be circumstances where other methods are indicated. The latter include intravenous injection, and depot therapy (which may be either subcutaneous or intramuscular). Some alteration in the structure of the œstrogen may be required to render it suitable for such purposes. For example, stilbœstrol is relatively insoluble and has to be converted to an inert soluble compound (stilbœstrol diphosphate, Honvan) to make it fit for intravenous use. This is achieved by phosphorylation which has the added theoretical advantage of encouraging temporary concentration of the compound at the sites of phosphatase activity with the liberation of pure stilbœstrol. The same principle of phosphorylation has also been applied to the natural derivative œstradiol, and the resulting product Estradurin has been used with success by intramuscular injection (Jönsson *et al.* 1957). Other forms of depot therapy, however, have proved disappointing on account of the relatively slow and inconstant rate of absorption.

At the present time experimental work is proceeding with what are termed 'non-œstrogenic œstrogens'. This apparent contradiction in terms applies to substances which are potentially capable of promoting tumour suppression without inducing hormonal effects. This deviation of endocrine control towards the general realm of cancer chemotherapy is somewhat speculative and for the moment it seems best to rely on preparations which at least provoke some signs of feminization.

Most of the foregoing methods have been tried in the present series and the following conclusions have been reached. In general, oral administration is preferred as this can be easily varied or, if necessary, stopped if complications supervene. Stilbœstrol remains the preparation of choice and there seems nothing to be gained by alternation with other synthetic compounds. The substitution of a natural derivative (such as ethinyl œstradiol), however, will occasionally diminish nausea and other general side-effects, but tumour control is liable to suffer.

Short courses of intravenous œstrogens are frequently effective in securing the abatement of urgent symptoms and may also find some application in the treatment of chronic urinary retention. It must be remembered, however, that the latter will often continue to require surgical relief and the two forms of treatment should be regarded as complementary. In some cases a combination of temporary catheterization and intravenous Honvan will restore satisfactory bladder emptying and avoid the need for prostatic resection.

Prolonged intravenous therapy and also depot therapy require to be used with extreme caution owing to risk of overloading. This applies particularly to the latter where it may be difficult to counteract any adverse effect when once the œstrogen has been given.

With regard to timing, it is sometimes suggested that since the response may be only transient, treatment should be deferred to the late stage of the disease. This somewhat nebulous advice is difficult to apply and it has been our practice usually to give œstrogens at the time of diagnosis. The only exceptions have been in elderly patients with minimal symptoms and in those where a small and previously unsuspected focus of cancer has been found on routine examination of prostatectomy material. In other instances where cancer has been clinically evident before operation, full treatment has been instituted at once.

The view that œstrogens should be given immediately when symptoms occur is to some extent supported by a study of the survival

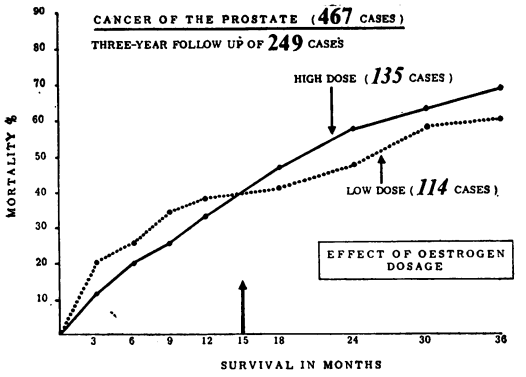

Fig 7 *Effect of œstrogen dosage; three-year follow up*

curves relating to the treated cases (Fig 7). Here it appears that the steep rise in mortality during the first year can be abated by intensive treatment. At this stage œstrogen dosage of the order of 100 mg stilbœstrol daily improves the chances of immediate survival. Prolonged treatment at a high level, however, brings with it the risk of certain complications which may well affect the ultimate prognosis.

Complications

Many of the hormonal side-effects of therapy are well known and such features as mammary hypertrophy commonly occur and even fluctuate, apparently irrespective of dosage. They are seldom of serious consequence but may prove annoying to the patient. In one case, after castration had failed to control the tumour, the alternation of stilbœstrol, TACE and Honvan only provoked increasing breast enlargement which eventually necessitated amputation.

It is not, however, with the feminizing effects that we should be mainly concerned but with the far more serious consequences of fluid retention and disposal of the products of œstrogen metabolism. These complications perhaps are less well recognized. The prolonged use of high doses of œstrogens can cause chronic fluid retention and lead to congestive cardiac failure. The risks involved with depot therapy are particularly obvious since the effect may continue; and the use of diuretics to decrease the load may only aggravate the urinary symptoms. The route of administration and level of dosage should thus be chosen with discretion especially in cases with evidence of decompensation; and in general it seems that the amount of stilbœstrol by mouth should be reduced after the first few months to a maintenance level of about 25 mg daily.

Similar observations apply to the avoidance of hepatitis which may occur through overloading the liver with the products of œstrogen metabolism. This complication has been seen on several occasions in the present series but only when exceptionally high dosage had been employed for a lengthy period.

On the whole, however, the incidence of serious complications has been remarkably small and when compared with the benefits that accrue œstrogen therapy must be accounted a successful form of conservative management.

Nevertheless the response is apt to be haphazard and in some cases transient, and the reason for this remains obscure. Analysis of the cases under review shows that it is unrelated to the histological pattern of the tumour and that there are no tangible means at present of gauging the initial endocrine dependence of the disease. The only prognostic factors at the outset are age and the presence of metastases – both of which need qualification.

Although the disease is often less active in the elderly and usually easier to control, the risk of death from other causes is naturally increased.

Radiological metastases, while certainly of adverse significance, carry a differential prognosis which is somewhat better than might be expected (Fig 8). This seems to confirm that the disease *as a whole* is capable of responding to hormone therapy.

In cases remaining controlled during the first few months the outlook becomes somewhat clearer and when once the first year is passed there is nearly a 50% chance of five-year survival. Most relapses occur within the first eighteen months and we may then be faced with the problem of deciding whether anything further can be done. I do not propose to dwell on the more elaborate methods of endocrine control save only to point out that the balance between risk and benefit is often small. Such measures as adrenalectomy and pituitary suppression remain largely speculative and there are no guiding features to indicate their probable effect.

With regard to the adrenal, attempts at medical suppression have generally proved abortive and I

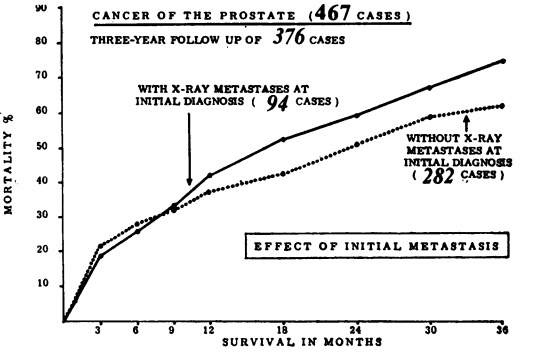

Fig 8 *Effect of presenting symptoms; three-year follow up*

know of no large series where consistent benefit has accrued. A distinction must be drawn between the euphoria induced by cortisone therapy and any possible symptomatic effect. Caution must also be observed lest some of the other hormones which have been employed may not actually stimulate the disease.

Adrenalectomy itself is sometimes capable of promoting tumour regression but the results in terms of survival have not generally been good enough to warrant the extended use of this operation in elderly patients. Furthermore it has now become outmoded by procedures to promote pituitary suppression. The results of the latter in a series of 50 of our own cases have recently been reported to the British Association of Urological Surgeons (Fergusson & Phillips 1962). The procedure of implanting radioactive material into the pituitary under X-ray television control (Fergusson & Stevenson 1960) can be rapidly accomplished and carries far less risk than any form of open surgery. Although destruction of the gland may be incomplete the symptomatic response is often dramatic and, on the whole, the extension of survival, in the advanced cases to which it has been applied, has been reasonably good.

Conclusion

Œstrogen therapy seems to be the most widely adopted method of endocrine control and, after twenty years, is in need of some reappraisal. In addition, the variable distribution and activity of the disease make the results of treatment very difficult to assess. Nevertheless when we remember that just over thirty years ago, before the introduction of endocrine methods (Bumpus 1926), most patients died of prostatic cancer within eighteen months we can feel assured that conservative management of this description carries at least some benefit.

Acknowledgments

In preparing this Address I have been greatly aided by the work of my successive Research Assistants at the Institute of Urology, Mr E C Gibson, Mr G F Murnaghan, Mr J R M Davidson and Mr D E H Phillips; by the staff of the Records Departments at the Institute and St Paul's Hospital; and by Mr P M Payne and his staff at the South Metropolitan Cancer Registry. The illustrations and tables were prepared by Miss F M Wadsworth and Mr R Bartholomew at the Institute and by Mr A Booker at the Central Middlesex Hospital. To all these and to my colleagues at St Peter's, St Paul's and St Philip's Hospitals and the Central Middlesex Hospital my thanks are due for their generous assistance and advice.

REFERENCES

Bumpus H C (1926) *Surg. Gynec. Obstet.* **43**, 150
Clifton J A, Philipp R J, Ludovic E & Fowler W M (1952) *Amer. J. med. Sci.* **224**, 121
Fergusson J D
(1946) *Lancet* ii, 551
(1961) *Brit. J. Urol.* **33**, 443
Fergusson J D & Franks L M (1953) *Brit. J. Surg.* **40**, 422
Fergusson J D & Gibson E C (1956) *Brit. med. J.* i, 822
Fergusson J D & Pagel W (1945) *Brit. J. Surg.* **33**, 122
Fergusson J D & Phillips D E H (1962) *Brit. J. Urol.* **34**, 485
Fergusson J D & Stevenson J J (1960) *Brit. J. Urol.* **32**, 484
Franks L M (1954) *J. Path. Bact.* **68**, 603
Jönsson G, Röhl L & Wiegner K (1957) *Acta chir. scand.* **113**, 68
Nesbit R M & Baum W C (1950) *J. Amer. med. Ass.* **143**, 1317

Meeting November 22 1962

The following cases and specimens were shown:

Four Cases of Cystine Urinary Calculi
Mr Edgar Freshman

Undifferentiated Carcinoma of Renal Pelvis Surviving Three and a Half Years
Mr Irvine Smith

Carcinoma of Renal Pelvis
Mr E J C Wynne

Extensive Partial Nephrectomy for Carcinoma in Solitary Kidney
Mr D I Hamilton (for Mr R Turner-Warwick)

Duplication of the Testis and Infertility
Mr J N Ward-McQuaid

A True Hermaphrodite with XY Chromosome Constitution
Mr J D Atwell (for Mr H L Duthie)

Perineal Testicle Before and After Operation
Mr H N G Hudson

Leiomyoma of Urethra
Mr S H C Clarke

Cancer of the Bulbous Urethra
Mr A E Thompson (for Mr H H G Eastcott)

Mid-line Sinuses of Peno-scrotal Skin
Mr C Wastell (for Professor H Ellis)