THE ROLE OF OESTROGEN THERAPY IN THE TREATMENT OF PROSTATIC CANCER

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Oestrogen therapy for prostatic cancer represents the logical application of certain principles derived from individual physiological and biochemical research to the field of malignant disease. Though the full extent of its potentialities remains uncertain, sufficient time has elapsed since its introduction to allow some evaluation of its merits; and to assess its relation to other methods of treatment. In analysing the findings, however, it must be remembered that the simplicity of the treatment has led to its application in many cases of unproven malignant disease, and that any claim of benefit or long-term survival arising from these must be interpreted with restraint. With this in mind it is felt that, in addition to a description of oestrogen therapy and its results, a few remarks on the differential diagnosis of prostatic cancer may not be out of place.

Historical

The rationale of oestrogen therapy in prostatic cancer is based on the assumption that the majority of tumours are composed of cells resembling those of adult prostatic epithelium in their capacity to undergo regression in response to oestrogens.

In 1935 an investigation into the origin of certain enzymes occurring in human urine led to the identification of the prostate as a prolific source of a phosphatase having its maximum activity in an acid medium (Kutscher and Wolbergs, 1935). This enzyme was believed to be identical with an acid phosphatase previously detected in splenic extracts (Davies, 1934), and in the spleen and kidney of certain herbivorous animals (Bamann and Riedel, 1934). Subsequent biochemical observations (Gutman and Gutman, 1938a) showed that the enzyme was only elaborated in quantity by the mature prostate gland, and this finding was later confirmed by staining methods (Gomori, 1941). In the meantime extension of the enquiry into pathological fields had led to the remarkable discovery that acid phosphatase production was abundant in many cases of prostatic cancer (Gutman, Sproule and Gutman, 1936). By inference these findings suggested that tumour cells resembled those of highly differentiated adult prostatic epithelium, at least in so far as elaboration of the enzyme was concerned. Further research indicated that in many cases of metastasizing carcinoma, where an increased production of this enzyme by the secondary deposits could now be anticipated, there was a corresponding rise in the acid phosphatase content of the blood serum (Gutman and Gutman, 1938b). This reflection in the serum of the activity of enzyme elaboration by metastatic growths has since been used as a confirmatory test for prostatic cancer.

Contemporaneously with these investigations it was shown that spontaneous cystic hyperplasia of the prostate in senile dogs underwent rapid involution following castration or oestrogen administration (Huggins and Clark, 1940), suggesting that tumours in which mature epithelial tissue preponderated might be responsive to androgenic procedures. These methods, previously used with indifferent success in cases of human benign prostatic hypertrophy (White, 1893; castration; Wugmeister, 1937; Kahle and Maltry, 1940 (oestrogens)) had only been applied on fewer occasions in the form of castration to cases of prostatic cancer (Young, 1936; Randall, 1942) with unconvincing results. The synthesis of substances of great oestrogenic activity and capable of oral administration (Dodd, et al., 1938) made further trial desirable, and a series of cases of advanced metastasizing prostatic cancer was selected to determine the effect of androgens on the one hand, and of oestrogens or partial deprivation of androgen (castration) on the other. The results proved of the highest importance in showing that, while androgens activated the tumour and initiated a sharp rise in the serum acid phosphatase value, oestrogens or castration produced an inhibitory effect with a corresponding diminution of enzyme in the serum (Huggins and Hodges, 1941). Other observers, among them Herbst (1942a) working independently, were soon able to report striking symptomatic improvement following the use of oestrogens, and similar findings, though in lesser degree, were reported in cases treated by irradiation of the prostate and testes (Munger, 1941).
From this brief historical survey it may be noted that the successful development of oestrogen therapy depended firstly on the inference that prostatic cancer cells, in many cases, had an affinity with those of normal adult prostatic epithelium, and secondly on the timely synthesis of oestrogenic substances. It must constantly be remembered, however, that some prostatic cancers appear to consist of undifferentiated cells and may be unresponsive, while in all cases other methods of treatment remain available, and indeed are frequently applicable.

**Differential Diagnosis of Prostatic Cancer**

In considering the application of oestrogen therapy to prostatic cancer in urological practice, it will be realized that a prerequisite to the satisfactory assessment of results will be the establishment of a proven diagnosis. While recognizing that, in a number of cases, rectal examination will provide almost unequivocal proof of the disease, the diversity and ambiguity of symptoms and local signs in others will not infrequently give rise to doubt. In such cases the irresponsible practice of commencing oestrogen therapy solely on presumptive evidence is likely to give rise to even more misleading clinical characteristics on subsequent confirmatory examination. It is, therefore suggested that the following diagnostic procedures should be applied, as far as practicable, to all suspected cases before giving oestrogens, and it will be convenient later to consider the effect of treatment on the various aspects of the disease with which they are concerned.

**Rectal Examination.** The rectal findings are of considerable importance not only from the point of view of diagnosis and gauging the subsequent response of the primary lesion to oestrogens, but also in influencing the choice of treatment. Differentiation from adenomatous hypertrophy is not always easy and the two conditions may coexist, though usually in such cases the adenomatous enlargement is only moderate. In a few instances (about 2 per cent. of enucleations) the diagnosis of carcinoma is only made post-operatively on microscopy of what was presumed to be a benign gland. It must also be remembered that malignant changes may develop in the residual prostatic bed after a previous enucleation of benign adenomatous tissue. In a personal series of 81 consecutive cases of prostatic cancer five patients had undergone supra-pubic removal of an adenomatous gland at a period ranging from 5-18 years previously. In any event the finding of single or multiple areas of contrasting hardness or irregularity in the prostatic area should always arouse a suspicion of malignancy and indicate recourse to confirmatory tests.

Difficulty sometimes occurs in distinguishing between the hard nodularity of a malignant gland and that due to prostatic calculi, and the position is not rendered easier by the fact that both conditions may coexist (6 per cent. of cases of prostatic cancer, Cristol and Emmett, 1944). In such cases, as in others, consideration of the size and extent of the lesion together with the degree of fixation may prove helpful and will, in addition, serve as a useful guide in estimating the subsequent local response to oestrogens.

An attempt should be made to correlate the local findings with the symptomatology, recognizing that the three usual methods of spread of the cancer may, in addition to causing urinary obstruction and sepsis, give rise to symptoms in the following manner:—

(a) Upwards and backwards, involving the seminal vesicles and resulting in an indurated mass feeling like a bull's head (‘cabeza de toro,’ Vernet, 1944), causing diminished sexual activity and occasional haemorrhia.

(b) Downward spread, involving the external urinary sphincter, causing incontinence.

(c) Spread to the posterior urethra and bladder neck, ultimately involving the mucosa, causing strangury and haematuria.

Careful examination repeated at intervals during treatment will give useful information as to the relationship between the local and symptomatic response.

In addition to prostatic calculi the following conditions may occasionally lead to diagnostic difficulties. Chronic and tuberculous prostatitis, low vesical neoplasms, occasionally rectal carcinoma, and rarely, on account of their usual occurrence at an earlier age, utricular cysts and sarcoma.

Finally it must be remembered that a prostatic cancer may lose many of its malignant characteristics during oestrogen therapy and in some cases seen for the first time after receiving treatment elsewhere, the local condition may prove unrecognizable.

**Radiography.** The detection of osseous metastases by radiography is of great value in confirming the diagnosis. Characteristically both osteoplastic and osteolytic deposits occur together, though in some instances a diffuse sclerotic form, closely resembling Paget’s disease, may involve a wide area of bone. The earliest deposits usually occur in the pubic rami, but no part of the bony pelvis is exempt, and metastases not infrequently spread rapidly in centrifugal manner to the lumbar spine and femoral necks. More distant secondaries in the ribs, humeri and skull tend to appear later, but sometimes develop early in conjunction with
a small or occult primary growth. In such an event, isolated cranial metastases may be responsible for the rare instances in which facial and ocular nerve palsies, offer the primary manifestation of the malignant condition.

Pulmonary and mediastinal deposits, noted on radiography, require differentiation from those resulting from other primary neoplasms. Negative findings do not exclude the presence of a neoplasm, and useful information concerning the presence of prostatic calculi and other conditions affecting the urinary tract may be obtained which call for modification of the diagnosis and affect the choice of treatment.

**Serum acid phosphatase estimation.** Attention has already been drawn to the occurrence of raised acid phosphatase values in the serum in cases of prostatic cancer, due to increased production of the enzyme by the secondary deposits as well as by the primary growth. Significantly high readings are obtained in roughly 80 per cent. of cases with bone metastases (Huggins and Hodges, 1941; Sullivan, Gutman and Gutman, 1942; Herger and Sauer, 1945; and Herbert, 1946), and to a considerably lesser extent in cases without demonstrable metastases. In general, it may be said that positive findings of over five King Armstrong units per 100 ml. serum offer good confirmatory evidence of metastasing cancer, while readings of over three units are suggestive. Care must be taken in the collection of specimens to avoid haemolysis which may cause a false high reading.

The following table shows the results in a personal series of 62 cases in which the serum value and radiographic findings were compared at the time of admission.

<table>
<thead>
<tr>
<th>Bone metastases present (35 cases)</th>
<th>Serum Acid Phosphatase over 3 units.</th>
<th>Serum Acid Phosphatase under 3 units.</th>
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<tbody>
<tr>
<td>Bone metastases not detected (27 cases)</td>
<td>29</td>
<td>6</td>
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In 57 cases in which an opportunity presented for comparing the serum acid phosphatase level with the histological character of the neoplasm, no statistically significant variation was noted with growths of differing pathological structure. Growths of predominantly adenocarcinomatous type preponderated, and many of the higher enzyme readings were encountered with these. There are comparatively few extra-prostatic sources from which a significant production of acid phosphatase is possible in man, though advanced hepatic disease and, rarely, osteitis deformans may promote a rise in the total acid phosphatase in the serum. Differentiation of any enzyme elaborated in such cases can now be determined in terms of heat stability and alcohol resistance (Herbert, 1946) or susceptibility to formaldehyde (Abul Fadl and King, 1947). The latter method seems particularly valuable in that formaldehyde inactivates any enzyme produced by the erythrocytes, and thus minimizes errors due to haemolysed serum.

In clinically doubtful cases the use of provocative doses of testosterone to induce a rise in the serum value has been advocated (Sullivan, Gutman and Gutman, 1942; Wray, 1945), but this method is obviously not without risk, and is rarely indicated.

Finally it may be mentioned that repeated estimation of the serum acid phosphatase is of some value as an index to the progress of the disease during subsequent treatment, though allowance must theoretically be made for variation in the secretory potential of the malignant cells and the pathological structure of the growth. It is also quite possible that small seasonal variations in enzyme production occurs, even in old age, though this is not yet established.

Estimation of the excretion of acid phosphatase in the urine is of no differential value in the diagnosis of prostatic disease (Burgen, 1947), and is probably insignificant in comparison with the serological findings as a guide to treatment.

**Biopsy.** Biopsy affords an opportunity for certain diagnosis, and may be carried out either upon the primary growth or upon any accessible secondary nodule or affected lymphatic gland. Many methods are available, but in dealing with the prostate itself either exploration via the perineum or per-urethral resection are usually employed. Success will depend in the former on the ability of the operator to direct an instrument at the affected area, and in the latter, on the spread of the growth to a position accessible to the resectoscope.

Occasionally opportunity may present for microscopical examination of prostatic tissue enucleated by the supra-pubic or retro-pubic route.

Any tissue obtained at biopsy should be subjected to routine microscopy, biochemical estimation of the tissue acid phosphatase, and acid phosphatase staining. Microscopy, in addition to confirming the diagnosis, will enable a determination of the pathological structure of the growth to be made—a matter of some value in affording a basis for comparison should subsequent biopsies be performed. The quantity of acid phosphatase present in prostatic tissue may be of similar importance in cases where successive biopsies are carried out during treatment, but owing to wide variation in the amount present in benign glands it is not a reliable index of malignancy.
The presence of acid phosphatase in secondary glands, however, is more significant, and extremely suggestive of a primary prostatic neoplasm—a finding which may prove helpful in cases in which routine microscopy is unable to distinguish the initial focus (Fergusson, 1946).

Having outlined certain methods of substantiating the diagnosis of prostatic cancer it will be noted that while each offers useful confirmatory evidence, none by itself is infallible. A combination of all practicable measures, however, will, in addition to establishing the diagnosis, give an accurate picture of the state of the disease upon which a correct choice of treatment can be based.

The Place of Oestrogen Therapy in Relation to Other Methods

Since at the present time there is no authoritative evidence of oestrogens causing complete regression of a confirmed prostatic cancer due regard must still be given to the relative merits of other methods of treatment, and the position of oestrogen therapy as an ancillary determined accordingly.

Broadly speaking when once a diagnosis of prostatic cancer is established, oestrogen therapy is applicable to every case; the risks and disadvantages of any side effects being more than compensated by the beneficial response. It remains, therefore, to consider how far previously recognized therapeutic measures can prudently be subordinated to the new method. In dealing with this problem three main aspects suggest themselves.

In the treatment of a localized early neoplasm. In view of the lack of evidence of complete neoplastic regression with oestrogen therapy, radical prostatectomy must still be regarded as applicable to a small number of early cases where no metastatic spread is demonstrable, and where the local mobility of the lesion and the general condition of the patient permits. Oestrogens are indicated as a pre-operative measure (Colston and Brendler, 1947). Unfortunately, few patients present themselves at a time when successful prostatectomy is practicable, and even when carried out there remains a risk of undetected metastases developing subsequently. The prognosis following radical surgery appears largely to depend on the degree of local autonomy already acquired by the growth at the time of operation; since when this is once established metastatic spread can be assumed probable (Masina, 1945). It is at present unknown whether oestrogens can reverse this process, but a prolonged course of post-operative oestrogen therapy is indicated to minimize potential metastatic activity. The hope has been expressed that in more advanced cases with metastases oestrogens might sometimes render an inoperable case suitable for radical cure. From what will be noted later with regard to the individual response of the primary and secondary lesions this notion is both ill-conceived and untenable.

In the relief of urinary symptoms. The greatest danger in connection with oestrogen therapy lies in it being regarded as a panacea for all urinary disturbances arising from prostatic cancer. It is in this sphere, more than in any other, that its relationship to other methods of treatment has to be considered. The evil consequences of urinary obstruction and sepsis demand that ample measures should be taken for their prevention and relief, and for this reason the use of oestrogens must often be regarded as supplementary to perurethral resection and chemotherapy. In the same way, occasionally, when a small malignant area is detected in association with predominant benign hypertrophy, prostatectomy by the supra- or retro-pubic route may offer the best chance of relieving urinary obstruction, and is still indicated even though metastases be present. The latter may subsequently be controlled by oestrogens. With lesser degrees of urinary obstruction, and very occasionally in cases of retention, it may be justifiable to rely on oestrogens alone (Rose, 1944) provided that a careful check is kept on the subsequent amount of residual urine by catheterization or excretion pyelography. Although the response to oestrogen therapy is often evident within a matter of days, it does not follow that the shrinkage of the prostatic epithelium thus induced is adequate for the relief of urinary obstruction, and adjuvant measures may be required. In a small number of cases with malignant fixation of the prostate, treatment with oestrogens alone has led to shrinkage of the gland with displacement of the internal meatus resulting in inadequacy of urinary control (Rose, 1944).

In general, a careful combination of anti-androgenic therapy and perurethral resection tends to give the best results in cases with urinary obstruction (Crane and Rosenbloom, 1945; Palomo, 1945; Nesbit and Plumb, 1946), and it may be said that palliative supra-pubic cystostomy drainage is now avoidable in all instances, save for the relief of urgent uraemia, and in cases of incontinence due to neoplastic invasion of the external urinary sphincter.

In the relief of metastatic symptoms. Prior to the introduction of methods of androgen control, the only available means of alleviating symptoms due to secondary deposits were irradiation, transfusion, and the use of anodynes, with frequently disappointing results. In this respect, as will be shown in a later section, the whole aspect of the disease has been profoundly altered. By the action
of oestrogens in suppressing neoplastic activity, pain and other symptoms dependent on metastatic involvement are frequently relieved to a much greater extent than can be attained by irradiation with its obvious limitations. In a few cases, however, when the tumour appears unresponsive, or where a delayed relapse occurs, recourse to irradiation and other methods previously in vogue is indicated.

Oestrogen Treatment

Having outlined the position of oestrogen therapy in relation to older methods of treatment it remains to consider its mode of administration and its efficacy in comparison with other methods of androgenic control.

Modern oestrogen therapy is concerned mainly with the oral administration of the synthetic oestrogens stilboestrol, hexoestrol and dienoestrol. Opinion varies as to which is preferable and as to the dosage to be employed. With regard to the former, personal case records show no significant difference in the results obtained from stilboestrol and dienoestrol, and alternation of the two has not produced any definite clinical change. Recently, however, the opinion has been expressed that stilboestrol may be slightly more effective (Morson, 1947). With increasing experience of the method, and with due regard to the side effects, the general tendency is to give larger doses than formerly, and I now give 15 mgms. oestrogen a day initially. The maintenance of a high dosage is also advisable (Cox, 1946) as it seems probable that this minimizes the risk of 'delayed reactivation' of the growth, and I have seen no ill effects from continuing the initial high dosage over periods of from two to three years. On the other hand, it is equally true that some cases do well on very low maintenance doses, but to apply this universally in the light of present experience seems to be taking an unnecessary risk unless troublesome side effects demand it. Further guidance with regard to the maintenance dose may be obtained from a joint consideration of the symptomatology and the serum acid phosphatase value.

The dosage advocated above is usually sufficient to produce a maximum effect on the symptoms, and requires no increase unless indications of 'delayed reactivation' of the growth appear later. It may, on the other hand, have to be reduced somewhat if side effects, particularly vertigo and nausea, prove troublesome. The incidence of tender enlargement of the breasts is not an indication for reduction of dosage.

Where the serum acid phosphatase value is very high when first estimated there may be a tendency to give larger initial doses, but these seldom seem to confer any additional benefit. In some cases it appears impossible to bring the serum value down to normal limits, and the maintenance dose is then best adjusted to a point at which it controls the symptoms and at the same time keeps the serum acid phosphatase value at a steady, though raised, level.

It has been the experience of many observers (among them Gilbert and Margolis, 1943; Nesbit and Cummings, 1944; Dean, et al., 1944; Huggins, 1946; Fergusson, 1946) that, after early and sustained improvement for some months with oestrogen therapy, a further outburst of activity of the disease may occur. Such cases of 'delayed reactivation' are often heralded by sudden loss of weight and are accompanied by a rise in the serum acid phosphatase value, together with the appearance of further metastases. In this event a drastic increase of the oestrogen dosage, to as much as 20 mgms. three or four times a day, is advisable, though unfortunately in the majority of cases even this will prove ineffective. My personal case records, however, include one instance of a patient receiving 10 mgms. oestrogen daily who relapsed and developed a complete paraplegia, without evidence of vertebral collapse, during the course of a few days some months after treatment commenced. Increasing the dose to 60 mgms. oestrogen a day was followed by almost complete recovery of sensation and function, and remarkable improvement in his general condition, which has now been sustained for eight months. The high dosage has been maintained throughout, without obvious ill effect.

A further case which relapsed after receiving 10 mgms. oestrogens a day for ten months, and showed indisputable evidence of rapidly advancing malignant disease with loss of weight and hourly frequency day and night, also responded to doses of 60 mgms. a day without additional measures. Lymphatic metastases disappeared, normal weight and micturition were restored, and he has since been able to resume an active occupation.

In view of the apparent loss of sensitivity to oestrogens in many cases showing 'delayed reactivation,' it has sometimes been advocated that treatment should be withheld in the earlier stages of the disease and used as a penultimate measure to combat the symptoms as they become uncontrollable by other means (Nesbitt and Cummings, 1944; Meads, 1945). With an irreversible form of treatment such as castration, in which the initial effect may not be long sustained, this may be advantageous, but in the case of oestrogens it seems a policy of despair, for, apart from the difficulty in determining the onset of the final decline, any prospect of early regression and a possible cure is thereby abandoned. It should, therefore, be the aim in all cases to commence and...
continue treatment in adequate doses from the time of diagnosis.

With regard to the relative merits of oestrogen therapy and castration, opinion varies in different parts of the world. The shrinkage of the testes, which usually accompanies the giving of oestrogens, appears almost tantamount to physiological castration, and the problem partly resolves itself into whether the patient can be trusted to continue taking his pills. Despite the similarity of clinical effect produced by the two methods there is, however, no doubt that the mode of action is different as shown by estimation of the oestrogen and 17 keto-steroid excretion in the urine in individual cases (Dean, Woodard and Twombly, 1944).

The main disadvantage of castration lies in the fact that the testes do not represent the entire source of androgen in the body, and increasing amounts of male hormone may subsequently be elaborated by the adrenals, necessitating supplementary treatment with oestrogens. Adrenalectomy has not become established as a practicable method of treatment in such cases (Huggins and Scott, 1945; Cox, 1947).

The psychological effect of orchidectomy is liable to be severe, and there is also a somewhat increased liability to flushings and vascular disturbances.

On the other hand, complete disappearance of bony metastases has been witnessed after castration but not after oestrogen therapy (Huggins, 1946), and it has been suggested that regression of the primary tumour is also more marked (Nesbit, Pazzos and Cummings, 1944). This view is not supported by other observers (Dean, Woodard and Twombly, 1944).

Neither method of treatment affords prophylaxis against a further increase of metastases, but pain occurring after castration has failed may sometimes be relieved by giving oestrogens. On the whole, in the majority of cases it seems that sufficient androgen control can be effected by giving oestrogens as to make castration unwarrantable in patients of average intelligence. In my own experience, castration, carried out in the stage of 'delayed reactivation' after oestrogens have failed, has not resulted in any improvement, though it may be justifiable if the testes have failed to shrink during the previous course of oestrogen therapy.

The Response to Oestrogen Therapy

The effect of oestrogen therapy can be measured subjectively or objectively according to the alteration in clinical symptoms and signs respectively, while more reliable evidence may be adduced from repeated performance of the same specific investigations used in the confirmation of the diagnosis. Ultimately the value of the method can be assessed by its ability to retard the progress of the disease and thus to increase the survival period—but this requires comparison with the results produced by alternative treatments, and is considered in a later section.

Symptomatic Response

It is convenient to classify symptoms according to whether they depend on urinary disturbance produced by the primary growth, or are associated with extra-urological metastatic foci. In the former case it is often difficult to ascribe improvement to oestrogens since other methods for the relief of urinary obstruction and sepsis may be adopted contemporaneously. In many instances, however, a marked reduction of urinary frequency and diminution of infection occurs when oestrogens alone are used. Such improvement together with better voiding and projection of the urinary stream is often noticeable within a few days of commencing treatment.

It is probable that the diminishing number of patients now requiring supra-pubic drainage is not altogether attributable to the extended use of perurethral methods and is, in great part, related to the employment of oestrogens. Similarly the need for repetition of perurethral resection appears considerably reduced thereby (Emmett and Greene, 1945).

With regard to symptoms due to metastatic foci, the experience of all observers points to oestrogen therapy being the most effective palliative at present known. In a personal series of 37 cases treated continuously with oestrogens, pain proved a notable feature in over 30, and symptomatic relief was obtained in 25 of these. Those failing to respond showed a resistance to oestrogens in other respects.

Asthenia, apart from terminal cachexia, is usually associated with marked anaemia due to widespread secondary deposits, and improvement following oestrogen therapy can be measured objectively by a rise in haemoglobin, and a fall in the erythrocyte sedimentation rate (Kearns, 1942). Restitution of the haemoglobin value to normal, in cases where it has previously fallen to below 50 per cent., is not uncommon.

Together with a progressive sense of well-being many patients notice a marked increase of appetite, and show a gain in weight. Where routine weighings are conducted gains of a stone or more may be recorded, but any subsequent loss is suspicious of 'delayed reactivation' of the disease. It is important to bear in mind that temporary water retention may occur when oestrogens are commenced (Herbst, 1942) and give rise to a misleading gain in weight as well as suggesting im-
improvement in urinary frequency. Deceptive alteration in weight may also be met with in connection with fluctuation in peripheral oedema due to malignant lymphatic obstruction.

Taking a general view of the symptomatic response to oestrogens it seems that about 80 per cent. of cases show initial improvement, which is sustained in 50 per cent. for over a year.

**Alteration in Clinical Signs**

Here again a distinction is conveniently made between the signs produced by the primary neoplasm and its metastases.

Characteristically, in cases responding favourably, local examination shows that the prostate gland tends to become smaller and softer, but seldom loses evidence of fixation if this has once been acquired. In a small series of 20 personal cases examined over a period of one year, 15 showed diminution in size of the prostate, 12 diminished hardness, and four, almost complete loss of malignant characteristics. Allowance must be made for subjective inaccuracies which are bound to obtrude, and examination carried out under standard conditions with the bladder empty. Coincidentally an improvement in the degree of any associated urinary obstruction and sepsis may be noted, and in some instances infected urine may become sterile.

Clinical evidence of metastasis may be apparent in the form of actual superficial glandular involvement or skin nodules, or in the development of external signs due to less accessible deposits.

Involvement of the superficial lymph glands is common in the late stages of the disease (about 20 per cent. of cases, Muir, 1934), and the response to oestrogen therapy is often most striking. Collections of hard discrete glands may resolve completely, in some cases, within two or three weeks, a feature which had led some observers to regard this form of the disease as being the most favourable to treat (Herger and Sauer, 1945). Skin nodules, on the other hand, are of greater rarity, though excellent results in connection with their disappearance after orchidectomy have been recorded (Huggins, 1946).

Disappearance of peripheral oedema due to extensive involvement of the pelvic lymphatics is sometimes seen during treatment, even though by the time it is manifest the disease has usually reached an advanced stage.

The response of certain neurological conditions is of considerable interest, and in addition to the case already described, several instances of partial or complete recovery from paraplegia, presumed due to metastasis, have been recorded (Clarke and Viets, 1943; Nesbit and Cummings, 1944; Alyea, 1945).

With regard to the occurrence of ophthalmoplegia or facial palsy, probably caused by osseous metastases in the skull, the prognosis appears less satisfactory, and no improvement was discernible in five personal cases despite increased oestrogen dosage.

Gain in weight and decrease of anaemia dependent on the generalized response of metastases have already been noted in the preceding section dealing with symptomatic improvement.

**Changes in Radiographic Appearances**

Many observers have recorded their impressions of radiographic improvement in the appearance of bone metastases during treatment, but in a number of instances the published results have been singularly unconvincing. Slight modifications in radiographic technique are sufficient to cause marked alteration in the definition of secondary deposits, and the increased sclerosis and disappearance of 'fluffiness' so commonly described, may in part be determined in this manner. Convincing evidence of complete regression of osseous metastases after castration has, however, been adduced in a few cases (Nesbit, Pazzos and Cummings, 1944; Huggins, 1946). Absence of visible improvement need not necessarily denote failure of the treatment since the radiographic opacity of secondary deposits may be partly irreversible.

A more general experience, however, appears to be a slow increase in the extent of the bone involvement (Moore, 1944), though often without any marked change in the clinical condition. It has been suggested that radiographic evidence of regression may be more marked in the earlier bone metastases adjacent to the primary growth, and that, as these tend to disappear, further deposits may occur more distally. No conclusive evidence has, however, been adduced in support of this view. On the whole, it appears that osseous metastases are somewhat resistant to sustained oestrogen control.

Regression of pulmonary and mediastinal lymph node metastases, according to radiographic evidence, has been reported in a few instances (Alyea and Henderson, 1942; Alyea, 1945).

A further application of radiographic methods in assessing the response of the prostatic lesion itself, consists in the repeated performance of lateral views of the pelvis with a balloon catheter in the bladder, thus enabling measurements of the gross size of the prostate to be made at intervals (Chute and Willetts, 1942). Natural fluctuations in the size of the gland associated with bladder neck congestion seem to render this method somewhat unreliable.

**Alteration in the Serum Acid Phosphatase Value**

The amount of acid phosphatase in the serum...
FIG. 1.—Serial biopsy specimens of prostatic carcinoma during oestrogen treatment, showing regression of tumour: (a) initial; (b) after 10 days; (c) 17 months later.

FIG. 2.—Sections from two similar axillary lymph-glands, affected by metastases from prostatic carcinoma, during oestrogen treatment. Gland (b) was removed 24 days after gland (a) and appears less malignant.

FIG. 3.—Serial biopsy specimens of prostatic carcinoma during oestrogen treatment, stained to show decrease in amount of acid phosphatase: (a) initial; (b) after a year.

FIG. 4.—Circumareolar pigmentation of male breast in patient receiving oestrogen treatment.
depends on the quantity elaborated by the primary growth and its metastases, and on the juxtaposition of blood vessels and the enzyme-secreting cells. There is no evidence at present to show that the growth factor and secretory potential of the neoplastic cells are necessarily interrelated, and widespread metastases may be associated with a relatively low serum acid phosphatase value. Similarly the serum acid phosphatase value does not bear a constant relation to the amount of enzyme present locally in the prostatic tissue. In general, however, including all types of growth, an abrupt reduction in the serum value is obtainable in about 75 per cent. of cases within a few days of commencing treatment. ' In patients showing a high serum acid phosphatase initially, the fall under treatment is the earliest objective sign that the tumours are sensitive to oestrogens ' (Herbert, 1946). From this observation the desirability of performing serum estimations before commencing treatment is at once apparent. As long as a satisfactory clinical response continues, the acid phosphatase value in the serum tends to remain at a reduced or normal level, but in cases subsequently showing ' delayed reactivation ' a further rise is usual—often before a change in the clinical signs is manifest. At this stage increased dosage of oestrogens, or supplementary castration, are usually unavailing in securing a further response.

Response of the Affected Tissues

From the scientific point of view repeated examination of affected tissue during treatment offers the most reliable objective indication of the effect of oestrogen therapy. The method is applicable either to the primary prostatic neoplasm, or to any accessible metastatic focus, but is limited in the latter by clinical considerations, and in the latter by the difficulty in obtaining comparable tissue on subsequent occasions.

Repeated prostatic biopsies during treatment have been carried out by several observers—in a small series over a period of two months (Schenken, Burns and Kahle, 1942), in one case over a period of 223 days (Heckel and Kretschmer, 1942), and in nine cases over a period ranging from ten days to three years (now 14 cases) (Fergusson, 1946).

In view of known variation in the histology of prostatic cancer (Young, 1936) certain precautions have to be observed in the performance of repeated perurethral biopsies so as to ensure that any tissue removed is suitable for comparison (Fergusson and Pagel, 1945), and care must also be taken in securing identical preparation of all sections for microscopy.

In patients showing clinical improvement the successive histological appearances have indicated regressive changes in the neoplasm (Fig. 1). These changes may be interpreted as showing alteration in the gross pathological structure of the neoplasm, together with cytological modifications including reduction in average size of the nuclei of the malignant cells. In general, neoplasms showing a predominantly adenocarcinomatous structure tend to become more scirrhous in type, with considerable reduction of the quantity of malignant tissue in standard microscopic fields. These changes have been described in greater detail elsewhere (Fergusson and Pagel, 1945).

Similar histological appearances have also been noted in the case of secondarily affected lymph glands removed at intervals during treatment (Fig. 2), but the opportunities for repeated glandular biopsy are infrequent owing to the rapid regression of this type of metastasis in responsive cases.

Supplementary evidence of changes in the affected tissue during treatment may be obtained by the examination of all biopsy material for acid phosphatase. This involves estimation of the enzyme in fresh tissue by means of direct biochemical assay, and by staining methods (Gomori, 1941). In cases responding favourably to oestrogens it is usual to find a considerable decrease in the amount of enzyme present in the later biopsies of the material (Fergusson, 1946) (Fig. 3), an observation which accords with the fall in the serum value.

One of the most remarkable features arising from the serial study of malignant prostatic tissue during oestrogen therapy is connected with cases showing ' delayed reactivation ' of the disease. It is a common experience in such instances to find that, despite obvious clinical evidence of rapid metastatic spread, the primary growth itself remains small. Examination of the prostate at autopsy not infrequently reveals surprisingly little malignant tissue, in comparison with that noted at previous biopsy, and in contrast with the actively malignant appearance of the metastases (Huggins, 1942 ; Gilbert and Margolis, 1943 ; Fergusson, 1946).

Having discussed the effect of oestrogen therapy on prostatic cancer it remains to consider any side effects which it may produce on other tissues before proceeding to an assessment of its ultimate effect on the survival period.

Side Effects of Oestrogen Therapy

It will be evident from the following remarks that, in cases where there is evidence of a satisfactory response by the growth, the benefit accruing will more than outweigh any of the disadvantages attendant on oestrogen administration.

Side effects may be considered in two groups—those affecting the urogenital system and accessory
reproductive organs, and those connected with disturbances of metabolism.

In the former group certain minor changes without clinical significance may be noted in the urethra and verumontanum, where the epithelium undergoes squamous metaplasia (Wattenberg and Rose, 1945). The same observers have also described the pathological changes commonly occurring in the testes and breasts during treatment. With regard to the testes, routine clinical examination reveals marked shrinkage in at least 25 per cent. of cases, and there is usually subjective evidence of a decline in sexual activity, which must not be confused with that occasioned by neoplastic involvement of the vesicles. It is surprising to note, on the other hand, that in a few cases treated by castration, ability to obtain penile erections has subsequently been restored (together with a capacity for contracting gonorrhoea) (Herbst, 1947).

Breast changes are almost the rule at some period during oestrogen administration, as evidenced by generalized swelling and tenderness, and occasional pigmentation of the areola, or rarely, the circum-areolar area (Fig. 4). Such changes frequently vary even though the oestrogen dosage remains unaltered, and in many cases ultimately subside. No definite prognostic significance can be attached to them. Pigmentation may also be observed occasionally in the mid line of the scrotum (Riches, 1944), and of the lower abdominal wall.

Change in complexion to a more feminine type, and deposition of fat in the supra-pubic region, are common.

 Vasomotor instability is stated to be more marked after castration than during oestrogen treatment (Rose, 1944) though mild degrees, with occasional vertigo, are not unusual with the latter. It is doubtful whether this can be connected with the rare occurrence of serious cerebral vascular disturbance of which several cases have been recorded. Such events are not uncommon in the age group under consideration, and may equally well be precipitated by erosion of a vessel by a cranial metastasis.

Synthetic oestrogens are stated to be metabolized by the liver with greater difficulty than the natural hormone (Herbst, 1947), and there are a few records of hepatitis occurring during treatment (Calhoun Stirling, 1945; Wattenberg, 1946). In such cases castration will prove preferable to continuing with oestrogens. Nausea and occasionally vomiting sometimes occur and call for a reduction in oestrogen dosage. The development of petechial rashes, possibly connected with hepatic disturbance, has been noted on occasions, but does not appear to be as common as in women receiving oestrogens for menopausal disorders.

Attention has also been focused on the adrenals in connection with their association with steroid metabolism and as sources of extra-genital andro-gen, but no definite clinical effects have been reported. Cases which have failed clinically to respond to anti-androgenic treatment, however, have shown adrenal enlargement at autopsy (Herbst, 1942b).

The initial administration of oestrogens may lead to retention of sodium chloride and water in the body in sufficient quantity to cause temporary oedema. It is unlikely that clinical evidence of this is often manifest, and attention has already been drawn to the possibility of confusion with
oedema due to secondary lymphatic involvement, or that associated with senile myocardial degeneration.

On the whole, the side effects which are liable to arise during sustained oestrogen therapy are seldom alarming, and bear favourable comparison with the disadvantages of other methods of treatment.

The Effect of Oestrogen Therapy on the Survival Period

Owing to its comparatively recent introduction the effect of anti-androgenic treatment on the duration of the disease cannot as yet be completely assessed. Preliminary reports, however, indicate an increase in the average survival period, and there is no doubt that the course is rendered more comfortable.

Alterations in the duration of the disease due to oestrogen treatment may be estimated by comparison with a control series of cases observed either contemporaneously or previously. Employing a contemporary control series Crane and Rosenbloom (1945), in a survey of 335 patients, concluded that the survival period was prolonged by one-third in 142 cases receiving oestrogens. Variations in the natural course of the disease, however, render such estimates unreliable unless careful statistical methods are employed. In this respect the work of Nesbit and Plumb (1946) is strongly commended to the reader’s attention as a model of accurate statistical research. The conclusion of these observers, based on a comparison of 125 cases treated since 1941 by anti-androgenic methods with 781 previous cases, was that the survival rates were significantly prolonged by endocrine modification.

One of the greatest difficulties in effecting an accurate comparison is that of being able to determine the time of onset of the disease. Elderly patients are notoriously unreliable historians of their own complaints, and it is frequently impossible to differentiate between symptoms caused by the carcinoma, and those due to coexistent benign hypertrophy or other disease. An alternative method to estimating the total duration of the disease is to compare the survival periods from the time of diagnosis. This, however, is only applicable in dealing with a contemporary control series, since new methods of diagnosis and increasing alertness in recognizing the disease serve to confirm the condition at an earlier stage in the more recent cases.

In the accompanying diagram an attempt has been made to combine records of the total duration and post-diagnostic duration of the disease in 81 consecutive cases of prostatic carcinoma treated during the past eight years.

The average duration of symptoms attributable to the disease up to the time of diagnosis was 8.2 months, a period considerably shorter than that occurring in other series (Bumpus, 1926; Nesbit and Plumb, 1946). Despite this, however, 18 patients were admitted with advanced disease and died within one month. The total duration of the disease in these cases averaged 8.5 months.

In the remaining 63 cases, 37 received sustained oestrogen therapy (supplemented by castration in three cases), five had intermittent or incomplete oestrogen treatment, and 21 received no oestrogen. All 63 cases were treated on standard lines in other respects, and were subjected to perirethral resection or prostatectomy (three cases) where indicated, on account of urinary obstruction. The following table gives the average duration of the disease from approximate onset to diagnosis, and from diagnosis onwards, in the three categories concerned.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Average duration of disease before diagnosis</th>
<th>Average duration of disease after diagnosis</th>
<th>Total duration of disease.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained oestrogen</td>
<td>7.3 months</td>
<td>10.3 months</td>
<td>26.6 months</td>
</tr>
<tr>
<td>therapy (37 cases)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermittent or</td>
<td>10.8 months</td>
<td>5.5 months</td>
<td>16.3 months</td>
</tr>
<tr>
<td>incomplete oestrogen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>therapy (5 cases)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No oestrogens (21 cases)</td>
<td>0.8 months</td>
<td>9 months</td>
<td>18.9 months</td>
</tr>
</tbody>
</table>

* 20 out of 37 cases treated with oestrogens are still surviving, so that a considerable increase in the ultimate average duration of the disease in this category can be expected.

It remains to consider whether the survival period of cases receiving oestrogen treatment may be affected by such factors as the initial serum acid phosphatase value, the presence of metastases at the time of diagnosis, and the pathological structure of the growth.

Initial serum acid phosphatase values

There are many variable factors to be considered before coming to any conclusion as to whether cases with greatly raised initial serum acid phosphatase values respond better to oestrogens. Excluding advanced cases dying within a month of commencing treatment, nine patients out of the 37 receiving sustained oestrogen therapy had initial serum values of over ten units (ranging between 11.6 and 154.9 units). The average duration of disease in these patients is, at present, 30.2 months—somewhat in excess of the mean figure.

Presence of metastases at the time of diagnosis

No satisfactory data can be obtained from the present series. Bone metastases were detected at
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the time of diagnosis in 23 out of the 37 cases receiving oestrogens, and in five cases superficial lymph nodes were affected. The extent of the secondary deposits was not uniform, and the response to treatment inconstant. The figures given by Nesbit and Plumb (1946), however, indicate, as would be expected, an appreciably lower survival rate in cases with metastases. Even so, their preliminary findings show that with oestrogen treatment the number of survivors at the end of two years is approximately double that of an untreated control series.

Pathological structure of the growth

In all except two of the 37 cases receiving sustained oestrogen therapy the histological structure of the growth has been examined—at initial biopsy (before commencing treatment) in 31, at autopsy in 14, and on two or more occasions during treatment in 14. Growths showing a predominant adenocarcinomatous structure have preponderated in the initial biopsies, while subsequent biopsies and the total autopsy material show a greater proportion of less cellular types. There is, however, no statistical evidence as yet to substantiate a clinical impression that neoplasms of predominantly adenocarcinomatous structure survive longer with oestrogens, though there is little doubt that the symptomatic response is more favourable.

In conclusion, it will be noted that, while oestrogen therapy offers an opportunity for reliving metastatic symptoms and prolonging the survival period, treatment of the primary growth largely remains a matter of urological concern. Furthermore, on reviewing the laboratory and radiological methods indispensable to a scientific assessment of the disease, the need for full cooperation of all concerned in the regulation of treatment is clearly apparent.

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