HORMONE THERAPY IN METASTATIC BREAST CANCER: CLINICAL RESPONSE AND URINARY GONADOTROPHINS

By

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ABSTRACT

The total urinary gonadotrophin output of a group of post menopausal women with metastatic breast carcinoma undergoing hormone therapy, which in every case initially consisted of treatment with diethylstilboestrol, DES (ca. 20 mg/d), has been studied for periods varying from seven months to \(3\frac{1}{2}\) years. No correlation between gonadotrophin output and clinical response was found, except that in all cases showing objective regression urinary gonadotrophin remained low throughout the remission period. A low level of gonadotrophin output was not, however, necessarily indicative of a good clinical remission. Following withdrawal of DES, and independent of the period of therapy, recovery to pre-treatment levels was the rule rather than the exception.

A small group of patients maintained on a lower dose of DES (3–5 mg/d) showed the same degree of suppression of urinary output as those receiving 20 mg/d, and several of these exhibited objective remissions.

The study has emphasised the importance of site specificity in the response to hormone therapy, and underlines the difficulties of relating the clinical response of the patient as a whole to changes in hormonal environment.

Attempts have been made in the past to correlate the pituitary gonadotrophin excretion in the urine of post-menopausal women suffering from breast carcinoma with the clinical response to hormone therapy (see e.g. Loraine et al. 1959). This work was done on a statistical basis and Loraine suggests that patients in the higher range of gonadotrophin output might respond less
favourably to diethylstilboestrol (DES) therapy than those in the lower range. Variation in the level of gonadotrophin output from patient to patient was so wide within the groups which showed a favourable clinical response and those which did not, that the prognostic value of a total gonadotrophin determination was doubtful.

The work to be described was aimed at examining both the short and long term effects of hormone therapy and in particular, that of DES on urinary gonadotrophin excretion in relation to the clinical response of metastatic breast carcinoma.

**MATERIAL AND METHODS**

*Urine Collection, Extraction and Assay*

Each urine collection consisted of a 48-hour specimen. Pre-treatment baselines were obtained from four consecutive 48-hour collections and thereafter 48-hour collections were made at intervals during the study. The extraction and assay of the gonadotrophic material was by the method of Loraine & Brown (1959). (For full details of the procedure used see O'Connor & Skinner (1964)). Urinary outputs of total gonadotrophins are expressed as mg HMG (First International Reference preparation).

**Hormone Therapy**

Two groups of patients were examined. The larger group of 18 patients had baseline determinations made before the start of DES therapy. The smaller group of five patients were selected on the basis of a classical clinical response to DES and no pre-treatment levels are available in these cases. All patients were approximately five years or more post-menopausal (Cole 1961) and none had been given previous hormone therapy.

In the larger group DES was continued either until the end of clinical remission or until it was established that no remission was being obtained. On withdrawal of DES, where clinically acceptable, a period was allowed to elapse before trial of another hormone. It is our experience that cases who respond initially to DES may show a further response on withdrawal and that such a withdrawal response might well be attributed to a subsequent drug if no interval were allowed. Thereafter, where deterioration was rapid, certain patients were given a trial on prednisone or, if deterioration was slower, then methylandrostenediol was tried, followed later by prednisone.

**Patients' regime**

Diethylstilboestrol: a routine oral dosage of 5 mg/d was used, increasing by 5 mg each week to a final dose of 20 mg/d by the end of one month. Any deviations from this are noted in the Results.

17α-Methylandrostenediol: 100 or 200 mg/d in tablet form.
Prednisone: 20 or 30 mg/d in tablet form.
RESULTS

Clinical Assessment

The clinical assessment of generally metastatic patients is difficult. Subjective assessment, being influenced by the nausea of stilboestrol, or the tonic action of androgens or of corticosteroids, is frequently inaccurate. Thus, only objective assessment (measurement of accessible disease, radiographic evidence) has been allowed. Even here difficulties arise in that metastases may be seen to regress in one site yet progress in another. In general, however, one can usually place cases within the classification utilized, viz:

(a) Definite regression of disease
(b) Arrest of disease previously extending
(c) Continued extension and deterioration

Case Histories

Two representative cases are described in detail to illustrate the correlation of clinical and biochemical findings.

Case No. 11, A. N. (See Fig. 1 and Table 1). Age at start of hormone therapy, 65 years (20 years post-menopausal)

Following two years’ history of a lump in right breast she had a radical mastectomy and post-operative irradiation to axillary, supraclavicular and parasternal regions, April/June 1957, at which time chest radiograph was clear. She remained well until October 1960 when skin recurrence appeared in the flaps and was excised (histology positive). A further skin recurrence was similarly dealt with in April 1961.

Fig. 1.
Table 1.
Data relating to clinical response and urinary gonadotrophin excretion before, during and after diethylstilboestrol therapy.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Initials</th>
<th>Age</th>
<th>Years post-menopause</th>
<th>The treatment period</th>
<th>The withdrawal period</th>
<th>Gonadotrophins returned to ca. pre-treatment level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean gonadotrophin excretion</td>
<td>Diethylstilboestrol mg/day</td>
<td>Duration of treatment (months)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pre-treatment (P)</td>
<td>Treatment (T)</td>
<td>P/T</td>
</tr>
<tr>
<td>1</td>
<td>HB</td>
<td>62</td>
<td>7</td>
<td>67.4</td>
<td>20.9</td>
<td>3.2</td>
</tr>
<tr>
<td>2</td>
<td>WAC</td>
<td>73</td>
<td>24</td>
<td>40.5</td>
<td>7.0</td>
<td>5.8</td>
</tr>
<tr>
<td>3</td>
<td>EAD</td>
<td>74</td>
<td>&gt;15</td>
<td>40.9</td>
<td>9.0</td>
<td>4.5</td>
</tr>
<tr>
<td>4</td>
<td>MD</td>
<td>62</td>
<td>7</td>
<td>78.0</td>
<td>22.0</td>
<td>3.6</td>
</tr>
<tr>
<td>5</td>
<td>EGE</td>
<td>65</td>
<td>11</td>
<td>46.0</td>
<td>5.8</td>
<td>7.8</td>
</tr>
<tr>
<td>6</td>
<td>BG</td>
<td>61</td>
<td>19</td>
<td>65.7</td>
<td>16.8</td>
<td>3.9</td>
</tr>
<tr>
<td>7</td>
<td>LH</td>
<td>50</td>
<td>6</td>
<td>110.9</td>
<td>20.1</td>
<td>5.5</td>
</tr>
<tr>
<td>8</td>
<td>PEK</td>
<td>68</td>
<td>25</td>
<td>51.4</td>
<td>11.0</td>
<td>4.7</td>
</tr>
<tr>
<td>9</td>
<td>HL</td>
<td>69</td>
<td>22</td>
<td>48.1</td>
<td>13.3</td>
<td>3.6</td>
</tr>
<tr>
<td>10</td>
<td>GI</td>
<td>55</td>
<td>10</td>
<td>2.1</td>
<td>1.5</td>
<td>1.4</td>
</tr>
<tr>
<td>11</td>
<td>AN</td>
<td>65</td>
<td>20</td>
<td>61.4</td>
<td>7.7</td>
<td>8.0</td>
</tr>
<tr>
<td>12</td>
<td>OMR</td>
<td>56</td>
<td>11</td>
<td>52.3</td>
<td>14.7</td>
<td>3.6</td>
</tr>
<tr>
<td>13</td>
<td>ER</td>
<td>66</td>
<td>&gt;10</td>
<td>58.5</td>
<td>15.8</td>
<td>3.7</td>
</tr>
<tr>
<td>14</td>
<td>MS</td>
<td>54</td>
<td>&gt;5</td>
<td>91.3</td>
<td>22.0</td>
<td>4.2</td>
</tr>
<tr>
<td>15</td>
<td>FFW</td>
<td>55</td>
<td>10</td>
<td>104.1</td>
<td>24.7</td>
<td>4.2</td>
</tr>
<tr>
<td>16</td>
<td>EW</td>
<td>57</td>
<td>4</td>
<td>91.5</td>
<td>7.7</td>
<td>11.9</td>
</tr>
<tr>
<td>17</td>
<td>GW</td>
<td>64</td>
<td>14</td>
<td>96.9</td>
<td>45.6</td>
<td>2.1</td>
</tr>
<tr>
<td>18</td>
<td>CW</td>
<td>70</td>
<td>&gt;10</td>
<td>21.5</td>
<td>10.8</td>
<td>2.0</td>
</tr>
</tbody>
</table>

D = Died during treatment with DES.
** Objective regression.
* Arrest of disease, with subjective relief.
Figures in brackets denote no. of estimations.
In October 1961 dyspnoea developed, and radiographs of chest showed multiple bilateral metastases with, in addition, a right sided effusion. After baseline studies she was started on DES. Six weeks later further radiographs showed disappearance of some of the pulmonary metastases, whilst others were smaller. Clinically she was much improved.

In February of the following year, after some trauma she complained of pain in right hip and radiographs demonstrated a sclerotic metastasis in the right ilium and a possible lytic metastasis in the pedicle of the third lumbar vertebra (L. 3). Unfortunately no previous films were available for comparison, but the sclerotic appearance of the iliac metastasis suggested a hormone-holding effect and DES was continued, clinical symptoms disappearing within three weeks. She remained well and symptom-free for a further 16 months; a routine chest radiograph in the interim (March 1963) showed no evidence of pulmonary metastases or effusion. Thereafter further pain developed in the hip, causing her to take to bed, and radiographs showed the previous sclerotic metastasis to be lytic. X-ray treatment was given to this lesion and DES (considered now to have lost any beneficial effect) was shortly withdrawn. At this time, however, chest radiographs remained clear and there was sclerosis of L. 3. When last seen (28. 7. 64), twelve months after withdrawal of DES, she remained symptomatically well, walking unaided; radiographs showed pulmonary fields to be still clear, ilium – considerable sclerosis and healing, L. 3 slight progression.

It is interesting to note that DES in this case has exerted a definite and lasting control over pulmonary metastases, a less definite control on skeletal metastases, and that whilst control was still being maintained in the former it was lost in the latter.

Case No. 2, W. A. C. (See Fig. 2). Age at start of hormone therapy – 73 years (24 years post-menopausal)

Following a four year history of an undivulged lump in the left breast she became rapidly dyspnoeic. Radiographs confirmed a large right sided pleural effusion and collapse of the 9th dorsal vertebra (D. 9). Although no malignant cells were recognised in a pleural tap it seemed reasonable to accept that the effusion was secondary to her breast carcinoma and after pre-treatment investigations she started on DES (17. 10. 61).

Within six weeks the breast mass showed considerable reduction in size, from 8 X 9 cm to 5 X 5 cm, and the effusion was likewise reduced. At 3½ months radiographs confirmed dramatic response of effusion and at 7½ months still further improvement, and also sclerosis of D. 9. The local mass then measured 4 X 4 cm.

She remained symptomatically well for a further ten months when, after a fall, she had increasing pain in left thigh. Radiographs demonstrated deterioration in D. 9, also further metastases in dorsal and lumbar spine, pelvis
and left femur. A radiograph of chest was, however, clear, and the local mass measured 6 × 7 cm. X-ray treatment was given to the worst of her skeletal metastases, and although DES still appeared to be exerting some control over local and pulmonary disease, as it might be aggravating the skeletal situation it was thought wise to withdraw it (25. 6. 63).

Three months later (17. 9. 63) the local mass had become so much less definite that it was rated as »difficult to measure« and radiographs showed sclerosis in metastatic areas not treated with XRT. The whole situation remained »in arrest« for a further nine months when ulceration (1.5 cm) appeared over the left nipple. Two months later, and when last seen (28. 7. 64) she was symptom free. The tumour plaque in the left breast was again measurable (6 × 6 cm) and the ulceration had extended slightly (2.0 cm). Radiographs showed effectively no change since 17. 9. 63.

It is interesting to note that a general improvement followed initial DES therapy, that skeletal control failed more quickly than that on local or pulmonary disease and, in fact, DES may even have been aggravating skeletal metastases. On withdrawal there was a definite improvement in local disease and skeletal disease, the latter still maintained and the former beginning to slip.

**Pituitary Gonadotrophin Excretion.**

*Diethylstilboestrol Administration and Subsequent Withdrawal*

(a) *Diethylstilboestrol therapy*

18 post-menopausal patients have been observed for periods varying from seven months to 3½ years (Table 1). DES at the routine dose level caused a
substantial reduction in the urinary gonadotrophin output in 17 of these cases but the fall in gonadotrophin output varied from 40–95\% of the mean baseline determination (see Table 1 and also Figs. 1 and 2); during the treatment period the lowered gonadotrophin output was maintained, but there were in some individual cases considerable fluctuations in the excretory output. The remaining case (No. 10, G. I.) had a very low mean baseline level (2.1 mg/24 h), which was below the limit of detection in some samples, and DES had no effect whatsoever upon this low excretion level.

(b) The period following diethylstilboestrol therapy

The withdrawal period: The withdrawal period was usually short and for this reason gonadotrophin estimations during it were frequently few. Of the 17 patients for whom a normal post-menopausal gonadotrophin excretion was observed in the baseline determination, 14 survived the treatment period, and in 11 of them post-treatment gonadotrophin output eventually reached levels in the same range as those in the pre-treatment period. The recovery of the gonadotrophin output took place during the withdrawal period in seven of these cases, but in the other four patients further drug therapy had already commenced before gonadotrophin recovery occurred. There is one instance (No. 7, L. H.) of an overshoot during the withdrawal period to approximately twice the baseline gonadotrophin output, but this was abolished by pituitary ablation.

Subsequent Drug Therapy

Of the 17 patients with normal gonadotrophins, seven were given methylandrostenediol at variable intervals after the withdrawal of DES. Three of these subsequently had high dose prednisone and a further three patients had prednisone after withdrawal from DES.

Methylandrostenediol

Urine collections were made in five of the seven cases available. In two cases (Nos. 13, E. R. & 17, G. W.) the gonadotrophin output remained low. However, the output for G. W. returned to pre-treatment range two months after methylandrostenediol treatment had ceased, which was 15 months after the withdrawal of DES, and remained there for 10 months to the time of writing. In two other cases, Nos. 16, E. W. & 5, E. G. E., the output remained in the pre-treatment range after returning to this level during the withdrawal period, but fell towards the end of the methylandrostenediol treatment period in the case of E. G. F. The fifth case, No. 14, M. S., exhibited a sharp rise to the pre-treatment range, but here methylandrostenediol treatment began only one month after the withdrawal of DES.
**Prednisone**

Urine collections were made in five of the six cases available. In one case, No. 1, H. B., which was moribund and which had not received methylandrostenediol therapy, the gonadotrophin output showed a sharp fall during treatment. One other patient did not receive methylandrostenediol and in this case the gonadotrophin output, which had already recovered during the withdrawal period, remained, on the evidence of one sample, unchanged after three weeks of prednisone treatment. Of the three cases which had received methylandrostenediol, in one instance the normal pre-treatment level was virtually unaltered, whereas, in the second case, No. 13, E. R. (see O'Connor & Skinner 1964) the reduced output of the DES treatment persisted to the beginning of the prednisone treatment period. It then rose rapidly to twice the pre-treatment range before settling at pre-treatment level towards the middle of the fifteen month period of prednisone therapy. In the third case, No. 17, G. W., the gonadotrophin output which was in the pre-treatment range when prednisone was begun, also exhibited a rise to twice the pre-treatment output and then subsided to the pre-treatment range.

**Preliminary Group Showing a Classical Response to Diethylstilboestrol**

This group comprises five patients. The results of the bioassays are shown in Table 2 and may be considered in conjunction with the mean gonadotrophin output during DES therapy for those patients shown in Table 1, where in all instances a clear objective regression is accompanied by a low mean gonadotrophin output for the treatment period. This is demonstrated using an arbitrary separation level of 20 mg HMG/d (see Fig. 3).

**Table 2.**

Urinary gonadotrophin excretion during the period of diethylstilboestrol treatment in patients showing a classical clinical response to the drug.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Initials</th>
<th>Age</th>
<th>Years post-meno-pause</th>
<th>DES mg/day</th>
<th>Mean gonadotrophin excretion mg HMG/24 h</th>
<th>Time after start of treatment (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>C</td>
<td>70</td>
<td>13</td>
<td>3</td>
<td>1.9 (4)</td>
<td>3 – 11</td>
</tr>
<tr>
<td>20</td>
<td>EM</td>
<td>59</td>
<td>10</td>
<td>3</td>
<td>2.8 (2)</td>
<td>10 – 13</td>
</tr>
<tr>
<td>21</td>
<td>N</td>
<td>68</td>
<td>18</td>
<td>5 – 15</td>
<td>7.4 (4)</td>
<td>18 – 29</td>
</tr>
<tr>
<td>22</td>
<td>ANe</td>
<td>68</td>
<td>25</td>
<td>5 – 20 – 15</td>
<td>3.2 (4)</td>
<td>2.5 – 8</td>
</tr>
<tr>
<td>23</td>
<td>EWi</td>
<td>67</td>
<td>15</td>
<td>5 – 15</td>
<td>3.3 (2)</td>
<td>9 – 15</td>
</tr>
</tbody>
</table>

Figures in brackets denote number of estimations.

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DISCUSSION

In the main group of patients treated by DES, numbers do not permit of any statistical approach to the inter-relation of clinical response and gonadotrophin excretion, although it might be mentioned in passing that, in agreement with the observations of Loraine et al. (1959) the mean gonadotrophin output levels of the patients quoted in Table 1 both before and during treatment appeared to be slightly higher in the group of patients showing no response to DES than in those who responded:

<table>
<thead>
<tr>
<th>Response</th>
<th>Mean Gonadotrophin Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-treatment (P)</td>
<td>Under treatment (T)</td>
</tr>
<tr>
<td>** and *</td>
<td></td>
</tr>
<tr>
<td>551.6/10 = 55.2</td>
<td>130.2/10 = 13.0</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>576.9/8 = 72.1</td>
<td>146.2/8 = 18.3</td>
</tr>
</tbody>
</table>

The significance of this observation is, however, uncertain when one considers the influence on the means of cases No. 10 (G. I.) and No. 7 (L. H.).

Attention has, therefore, been directed to behaviour patterns in individual patients: clinical progress and gonadotrophin excretion pattern in each instance being examined in relation to:

(a) Rate of initial suppression of gonadotrophin output

(b) The ratio of the pre-treatment level to the mean for the treatment period, P/T

(c) The fluctuation in gonadotrophin output during DES treatment

(d) The absolute mean level of gonadotrophin excretion during treatment.

No correlation was found in any of these categories except that in any in-
individual case of objective regression, once the gonadotrophin output had been reduced to the low level it tended to remain low throughout the period of remission. A continued low excretion did not, however, impute a continued remission, and the level may remain low during subsequent periods of arrest and deterioration.

Gonadotrophin excretion during subsequent drug therapy does not show any trend which can be related either to the drug employed or to the clinical condition of the patient. There are three cases which exhibit a considerable overshoot of the pre-treatment gonadotrophin level. In one instance (No. 7, L. H.) this occurs during the withdrawal period, and in the two others (Nos. 13, E. R. and 17, G. W.) it occurs during prednisone treatment following a continued low output throughout the methylprednisolone therapy.

Site specificity of metastatic disease is of interest. The fact that metastatic disease may remain confined to one tissue for long periods is generally recognised. Such site specificity suggests the presence of differing environmental resistance to metastases from tissue to tissue. This may in turn be influenced differentially by more general humoral agents and it is perhaps not surprising that, on altering the hormone balance of a patient by exogenous hormone (DES), metastases in one site may respond whilst those in another do not. The tonic effect on normal body mechanisms (Nicol et al. 1964) may have some bearing on this.

A general response, as in No. 2, W. A. C., is often observed initially, but later the picture becomes more confused by site selectivity. In No. 11, A. N. not only is there a different response between metastases in lung and those in bone, but there is also a difference in behaviour of metastases in bone alone (ilium/lumbar spine). Is this a function of age of metastases, or are there different mechanisms operating within the same type of tissue?

The fact that the behaviour of metastases in different sites is inconsistent and cannot be related to the relatively consistent low level of «treatment gonadotrophins» suggests that the levels of total gonadotrophins has no direct relation to the metastatic spread.

The further evidence that remissions may follow the withdrawal of the drug again substantiates the lack of correlation between an improved clinical condition and a lowered gonadotrophin output. Indeed, from the clinical standpoint the change of hormonal environment may be the important factor.

What does seem apparent is that in such studies of clinical response to hormone therapy attention should perhaps be turned from the consideration of patient response as a whole, to specific sites of response within individual patients.

Considering now the observed lower gonadotrophin excretion during objective remission, it must be noted that certain cases, such as No. 10, G. I., can show an objective regression during DES therapy, although gonadotrophins
were barely detectable both before and during treatment. In three further cases not mentioned in the results, a barely detectable, or very low gonadotrophin output (<5 mg/d) was observed prior to anterior pituitary ablation. In one case there was no clinical response but of the other two, one showed an objective remission for four/five months and the other for sixteen/eighteen months. Such results again suggest that changes in endogenous gonadotrophin levels are of little importance in relation to regression of disease. In some moribund patient a low gonadotrophin excretion has been observed (see also Martin 1964), again adding to the difficulty of interpretation of low values.

The routine daily dose of DES used in this study was 20 mg. Suppression of gonadotrophin output is, however, achieved at lower doses, cf. Table 1, No. 9 (H. L.) 5 mg/d, Table 2, No. 19 (C.) and No. 20 (E. M.) 3 mg/d, all of whom showed objective regression. Other biochemical changes, e.g. increased plasma corticosteroids (Plager et al. 1964) are produced by doses of this order. These effects suggest that low dose therapy is perhaps acceptable. Certainly failure to tolerate high dosage should not indicate the abandonment of DES therapy.

It is evident from cases reported here and earlier (Skinner & O’Connor 1964) that DES does not destroy the capacity of the hypophysis to produce gonadotrophin even though treatment at the high level of 20 mg/d has been maintained for almost two years (No. 11, A. N.). Recovery of gonadotrophin secretion to the pre-treatment level is the rule rather than the exception, although a considerable time lag may occur, as in case No. 17 (G. W.). Since the effect of DES is not irreversible in respect of gonadotrophin secretion and a further suppression follows subsequent DES therapy (see Skinner & O’Connor 1964), if gonadotrophin levels play any part in remission of disease subsequent courses of DES might be expected to result in further remissions. However, when a first course has been continued to the end of remission, a second course seldom, if ever, gives a further remission.

No evidence has been produced here as to the mode of action of DES. Further examination of total gonadotrophins alone would not appear to be fruitful; it is felt that a much fuller assessment of hormone balance both in relation to general hormone patterns and also in relation to local tissue physiology, is required if observed DES effects are to be explained.

REFERENCES


Received on May 28th, 1965.