STILBOESTROL IN LATE MALIGNANT DISEASE OF THE BREAST.

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The value of synthetic oestrogen in carcinoma of the prostate is now widely recognised. The pain of bone secondaries in such patients is usually materially reduced, and it is generally accepted that in most cases there is prolongation of life with freedom from severe pain.

The possibilities of these drugs in late inoperable carcinoma of the breast are much less widely known. Generally surgeons and radio-therapists feel that the patient is in a hopeless and helpless position and must rely on sedation. It has been shown, however, that a small but fairly constant proportion of these women can have relief of pain and prolongation of life with oestrogen therapy, similar to that obtained in prostatic neoplasm.

This infrequent use of oestrogen may in part be due to the publication, from time to time, of papers suggesting that these hormones have carcinogenic properties.* In 1932 Lacassagne showed that oestrone could cause mammary carcinoma with great regularity in male mice of cancer-prone stock. Recently Moore *et al.* (1945) showed that during the administration of oestrogen for carcinoma of the prostate there is a proliferation of the mammary duct epithelium similar to that preceding malignancy. There does not, however, seem to be any case on record where the development of a malignant growth in the human could be ascribed to oestrogen therapy.

The first indication of a possible anticarcinogenic factor in the sex glands came in 1940, when Lewis treated 28 cases of malignant disease by the injection of an extract of fresh macerated bovine ovaries and testes. In all cases the growth regressed, with relief of pain when present, but appeared to progress with increased malignancy on stoppage of treatment. No cures were claimed.

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* Pioneer work was done in Glasgow by Beatson (1911), who claimed that bilateral oöphorectomy could cause regression of inoperable carcinoma of breast lasting up to 5 - 6 years, especially in young women with slowly growing and non-metastasised growths.

The use of oestrogen in breast cancer first appeared in British literature in the autumn of 1944, when a paper by Haddow *et al.* was succeeded by a discussion of the subject at the Royal Society of Medicine (1944). Reports on the results of treatment in a total of 204 patients were published. No cures were claimed, but 54 (26.5%) showed improvement in signs and symptoms for periods ranging from one to nine months; relapse occurred eventually whether therapy was continued or not. A small proportion—less than 5 per cent—seemed to deteriorate more rapidly when treatment was started. In the remaining cases no response of any kind was noted. In the same year Binnie gave details of four patients treated by oestrogen after radiotherapy; one of these cases responded very well and showed no sign of recurrence after nine months.

The daily dose of stilboestrol in patients in the above groups averaged just under 10 mgm. per day, usually in three divided doses, but the conclusion was reached that the optimum dose was about 15 mgm. per day. Larger amounts tended to cause side effects. Dienoestrol was found to have approximately similar effects in doses of 3 - 5 mgm. per day and to be slightly less toxic.

Toxic effects of a serious nature were rare. During treatment there tended to be a depressant—almost sedative—effect. Nausea, slight generalized oedema, and pigmentation of the areola were also noted.

Oestrogen was found to be most useful in cases of ulcerating neoplasm. Cases which responded successfully showed a rapid healing of the ulcer with relief of pain. This was in agreement with the earlier work of Heiman (1940), who showed that the administration of oestrogen to rats with transplanted mammary tumours appeared to stimulate epithelial growth, while testosterone inhibited it, in the tumour. He also showed that the oestrogenic action was much the more powerful of the two.

Previous radiotherapy did not appear to affect the response to stilboestrol therapy in the human, but the age of the patient had a considerable bearing on the result. For example, during the discussion already referred to the following figures were quoted:—

Age	No. of cases	Improved	Improved per cent
Under 60 years ..	100	14	14
Over 60 years ..	68	27	39.7

With a reported improvement rate for all ages of almost 25 per cent it seemed worth while administering oestrogen to cases of inoperable carcinoma rather than prescribe sedatives alone. A small series of breast cases has been so treated at the Eastern District Hospital, Glasgow, and brief notes of the results obtained are appended.

CASE SUMMARIES.

CASE 1. L. C., aged 76. admitted on 27th June, 1944, with a small malignant ulcer of breast of one month's duration. No glandular involvement. The ulcer progressed very slowly but by 7th September, 1945, had become a large, fungating mass almost replacing the breast tissue and the patient was deteriorating rapidly. On that date stilboestrol, 15 mgm. per day, was started. A fortnight later the ulcer was greatly decreased in size and by late December had healed completely. Six-week courses of stilboestrol in the above dosage were started on 7th September, 1945, 22nd December and 2nd May, 1946. On 4th July, she was transferred to an Old Age Home with no sign of local recurrence or of metastatic deposit.

On 29th October, 1947, the patient was still alive and in good health for her age. There was no sign of recurrence or metastases although she had had no further treatment.

The general depressant action of the drug was very noticable and very valuable in this case. Normally she was restless and had to be almost continuously sedated, but during the courses of stilboestrol this was unnecessary.

CASE 2. A. McG., aged 94. Admitted 7th November, 1944, with a large fungating ulcer of the breast of nine months' duration; no apparent glandular involvement. She had no specific treatment till 28th September, 1945, when it was apparent that she was deteriorating very rapidly. Stilboestrol was started in doses of $7\frac{1}{2}$ mgm. per day, and during the next two months the ulcer became cleaner and remained static in size. There was then complete relapse and death occurred on 4th February, 1946.

CASE 3. A. McA., aged 56. Admitted 4th January, 1946, with gross untreated cancer en cuirasse of six months' duration. Shallow ulceration was commencing and the general condition was very bad. Stilboestrol 15 mgm. per day started on 6th January without effect: died 18th January.

CASE 4. J. Cr., aged 67. Admitted 7th March, 1946, with a foul, fungating cauliflower mass replacing the right breast. History of radiotherapy for cancer of that breast with axillary metastases in September, 1944. She had severe pains in the back and limbs, and X-ray showed multiple bone secondaries. Stilboestrol, 15 mgm. per day from admission rapidly gave partial relief of pain but failed to alter the local condition, and death occurred on 18th April, 1946.

CASE 5. M. D., aged 72. Admitted to Western District Hospital in June, 1946, with malignant ulceration of breast measuring $4'' \times 2\frac{1}{2}''$, of one year's duration. Stilboestrol 6 mgm. daily started on 30th September, and increased to 15 mgm. per day on 23rd January, 1947, when the ulcer was cleaner and measured $2'' \times 2''$. An X-ray, however, now showed mediastinal secondaries which had not been present on admission. The local lesion remained unchanged from then until her death on 3rd October from exhaustion and terminal broncho-pneumonia.

This patient showed a marked symptomless jaundice while on oestrogen therapy.

CASE 6. C. G., aged 70. Mastectomy and radiotherapy for confirmed carcinoma of breast in the autumn of 1945. Admitted on 1st August, 1946, with 3-4 stony-hard, fixed and very painful glands in the ipsilateral axilla. She was given stilboestrol in doses rising from an initial 5 mgm. per day to 15 mgm. per day after three weeks. By then she was pain free and the glands almost impalpable. Treatment was stopped and she then developed a uterine haemorrhage for which no local cause could be

found. The bleeding gradually stopped and on 12th November she left the hospital feeling well and with no glands palpable in the axilla.

It has proved impossible to follow up this case.

CASE 7. J. Gil., aged 62. Admitted 26th June, 1947, with a tender mass occupying the whole right breast plus tender glands in the axilla, the condition being of 7 months duration. Biopsy confirmed the diagnosis of adenocarcinoma. Stilboestrol, 15 mgm. daily, was started on 9th July and within 10 days had given complete relief of pain. She left hospital against advice on 28th August still pain free and with no apparent alteration in the local condition.

On 6th January, 1948, she was seen as an out-patient, in very poor condition, and with considerable pain, which had recently recurred. No oestrogen had been taken since discharge.

CASE 8. R. D., aged 68. Had radical mastectomy and deep X-ray therapy in September, 1946, for scirrhus carcinoma of breast with axillary gland involvement. Admitted 25th February, 1947, with severe pain in the left leg and right arm, and a bone metastasis was visible radiologically in the latter position. No evidence of local recurrence. 15 mgm. of stilboestrol daily gave almost complete relief of pain in a week and the patient felt so much better that she insisted on leaving the hospital. She remained pain-free for 3 months without further stilboestrol, then was admitted to another hospital. More stilboestrol was given without effect on pain and she died on 15th November.

CASE 9. C. J., aged 50. History of pain in left breast for 6 years and had been having repeated courses of X-ray therapy for 3 years. Admitted 25th March, 1947, in very poor physical condition with multiple nodules in the breast and superficial ulceration, while large gland masses were palpable in the left axilla. Biopsy confirmed the diagnosis of scirrhus carcinoma. Courses of stilboestrol, 15 mgm. per day, and of dienoestrol, 6 mgm. per day, had to be abandoned as both drugs caused vomiting and vaginal bleeding after 48 hours. The patient died on 12th July in another hospital to which she had been transferred for further radiotherapy.

CASE 10. J. W., aged 76. Radical mastectomy and radiotherapy, 7 months before admission on 27th May, 1947, for a confirmed carcinoma of 2 years duration. She had extensive cancer en cuirasse with superficial ulceration in the mastectomy scar and severe lymphoedema of the arm. Full courses of dienoestrol (9 mgm. per day) had no effect on the neoplasm and failed to relieve pain. Died on 31st July.

CASE 11. A. B., aged 56. Admitted 17th May, 1947, with scirrhus carcinoma of the whole left breast extending subcutaneously to involve the medial half of the right breast. Duration about 5 years, and had had repeated courses of X-ray therapy. There was superficial ulceration over an area $3\frac{1}{2}'' \times 3''$ on left breast. Stilboestrol rapidly caused anorexia and nausea and was replaced by dienoestrol, 9 mgm. per day. This caused no side-effects; the ulcerated area became cleaner and was reduced to $3'' \times 2''$ by 9th June, but a pulmonary metastasis with effusion had appeared. The latter was uninfluenced by the drug and caused death from broncho-pneumonia on 27th August, with the breast condition still apparently improving.

CASE 12. M. W., aged 55. Gross cancer en cuirasse with mediastinal, axillary and skin metastasis; right mastectomy and radiotherapy 18 months previously. Stilboestrol, 15 mgm. per day, started on admission on 30th May, 1947, and changed to dienoestrol, 9 mgm. per day, on 10th June because of vomiting. No effect on local growth, on metastases or on pain; died on 24th July.

TABLE 1.

Case No.	Age	Duration before Treatment	Presenting Feature	Treatment before Hormone Therapy	Effect	Survival
1	76	1 year 4 months	Single ulcerated growth	Nil	Apparent cure	Alive and well in 2 years +.
2	94	1 year 7 months	Single ulcerated growth	Nil	No further growth	Death 4 months.
5	72	1 year 3 months	Single ulcerated growth with mediastinal glands	Nil	Regression of ulcer	Death 1 year.
6	70	1 year	Recurrent axillary glands	Mastectomy and radiotherapy	Regression of glands	Not known after 3 months.
7	62	7 months	Mass in breast and axillary glands grossly enlarged	Nil	Relief of pain	Alive after 6 mths., but condition poor.
4	67	1 year 6 months	Mass in breast with axillary glands and bone secondary	Radiotherapy	Partial relief of pain	Death 6 weeks.
8	68	Over 5 months	Multiple bone metastases	Radical mastectomy and radiotherapy	Relief of pain	Death 8½ months.
3	56	Over 6 months	Cancer en cuirasse	Nil	Nil	Death 12 days.
9	50	6 years	Cancer en cuirasse	X-ray therapy over 3 year period	Toxic effects requiring stoppage of hormone	Death 4 months.
10	76	2 years 7 months	Cancer en cuirasse	Radical mastectomy and radiotherapy	Nil	Death 2 months.
11	56	5 years	Cancer en cuirasse	Repeated courses of X-ray therapy	Regression of ulceration	Death 3½ months.
12	55	2 years +	Cancer en cuirasse	Radical mastectomy and radiotherapy	Nil	Death 6 weeks.

DISCUSSION.

This series of cases, as presented in Table 1, brings out several points worthy of comment.

(1) The two patients in whom the best results were obtained, and who survived a year or more (Nos. 1 and 5), were both over 70 and had a single, ulcerated growth. This is in agreement with the published findings, that ulcerative types of neoplasm in aged patients give the best results.

It is, however, also in patients with a single growth that surgical treatment has the best results, if seen at a reasonably early stage. Analysing a large personal series of cases, G. Gordon-Taylor (1938) found that surgery gave a 10-year survival rate of 84 per cent if the carcinoma was confined to the breast tissue and a 5-year survival of 40 per cent when local invasion had occurred.

Oestrogen therapy may have its place in patients frail and over 70, surgery being undertaken if no response occurs in 2 - 3 weeks and if the growth is single and with no or small axillary metastases.

(2) This short series of cases differs from those previously published in that it contains one apparent cure of an ulcerating growth, clinically a scirrhus carcinoma. It is unfortunate that no biopsy was performed and histological confirmation as a result is lacking.

(3) Of the remaining 11 patients seven showed some response to the hormone. Three had complete or partial relief of pain out of the five in which this was a marked symptom. The primary growth regressed in two patients and became static in another, while one case showed marked regression of axillary metastases.

The limitation of action of stilboestrol in cancer is, however, brought out by the fact that in only two cases did the response to it exceed two months.

(4) Toxic effect necessitated the withdrawal of hormones in one case and minor toxic reactions were not uncommon. Gastric upset occurred in 3 cases and vaginal haemorrhage in 2. The phenomenon of uterine haemorrhage on withdrawal of oestrogen is a well-known occurrence, the hormone being responsible for continued endometrial proliferation. This bleeding occurred in Case 6. It requires no special treatment but could be a formidable complication in a cachectic patient. Lactation was observed in Case 1 only, after her first course of treatment, and caused some mental distress; it did not recur in subsequent courses. Most of the cases developed a peculiar 'pasty' complexion which was by experience found to be characteristic of patients receiving oestrogen, and in Case 5 this was exaggerated to an actual icteric tinge of the skin.

(5) It was found that if relief of pain and/or regression of a malignant ulcer was not evident in one or two weeks practical benefit was unlikely to accrue.

(6) It seems worthy of comment that all the cases of cancer en cuirasse lay in the decade 50 - 60 years. Their very poor response to oestrogen is also apparent.

SUMMARY.

Carcinoma of the breast treated with stilboestrol has been reported to have an improvement rate of almost 25 per cent in cases where surgery and radiotherapy are unavailing.

This treatment can be given orally without strict supervision and the toxic reactions are not severe.

Twelve cases of inoperable malignant disease of breast are described in which oestrogen therapy was undertaken. Only four failed to show any response at all to treatment and three of these were almost moribund when first seen. One apparent 2-year cure was obtained, the patient being still alive.

A possible co-relation between the roles of surgery and hormone therapy in the elderly is suggested.

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