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HORMONE TREATMENT OF DISSEMINATED BREAST CANCER

BY

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In the endeavour to control malignant disease, clinical and experimental work is being carried out to find substances which will inactivate cancer or reverse the cancerous changes back to normal. There is evidence that by alterations brought about in the hormonal status of the body by various methods the cancerous process in certain patients can be checked, thus enabling them to live on for a number of years in excellent health. By this means a form of treatment is being developed which may enable us to attain our object, and ultimately it seems likely that hormone therapy will play an important part in those cancers which are hormonal-dependent. At present new methods are required for biological assays of hormones to provide us with scientific measurements of the changes which are brought about by various stages of cancer and the effects of hormonal treatment. We could thus measure the hormonal balance of the body and abnormal amounts of particular hormones, and determine the constitution of abnormal hormones which may be present. Treatment to-day is largely empirical, based upon clinical observations, and further advances will be made in our search for the truth when the laboratory comes to our aid in this way.

The presence of disseminated breast cancer creates a serious situation for the patient and a difficult problem for the surgeon. Until recent years the prospect was gloomy, but now a little gleam of light is showing. A number of workers have demonstrated that some of these patients are sensitive to variations of their sex

hormones; for regression in the disease has occurred with oophorectomy, adrenalectomy, and the administration of either androgens or oestrogens. This important therapeutic progress is not reviewed here; the object of this paper is to record the effects in a group of patients and especially to call attention to those patients who are living in excellent health more than four years later. The case record of the first patient has already been published (Raven, 1950); her subsequent history is now reported.

Case 1

A married woman aged 50 was seen on April 13, 1948, with disseminated carcinoma of the left breast. She stated that the various lumps became bigger just before her menstrual periods. A carcinoma 3.5 cm. in diameter was present in the upper inner quadrant of the left breast, with enlarged cervical and left axillary lymph nodes, the latter being fixed. Numerous skin deposits were present in the region of the left shoulder, left arm, chest wall, and right loin. A nodular lump 3.4 by 2.2 cm. was present in the right pre-auricular region. Histological examination of a cervical lymph node and a skin nodule showed spheroidal-cell carcinoma.

I performed a bilateral oophorectomy on July 7, 1948. The disease gradually disappeared, and on February 22, 1949, I found no evidence of cancer. The 17-ketosteroids in the urine were normal in January, 1950. In January, 1951, I excised a group of enlarged right axillary lymph nodes. Histological examination showed nodes replaced by sheets and cords of closely packed anaplastic polyhedral carcinoma cells. On January 8, 1952, an enlarged right supraclavicular lymph node and two small skin nodules in the posterior aspect of the chest were found; the patient was given methyltestosterone, 50 mg. daily, and these lumps regressed. The testosterone was withdrawn on July 28, 1953. Radiological examination of the chest and cervical, dorsal, and lumbar parts of the spine and pelvis was always negative for metastases. On December 22 I found a cyst 4 cm. in diameter in the left breast, and there was no clinical evidence of cancer anywhere. The patient is well, lives a normal life, and I think she looks younger than before, with colour in her cheeks: she volunteered the information that the latter was new for her, as she was always pale before the treatment. The amount of hair on her face has now decreased markedly, but her voice remains at a lower pitch than normal.

Case 2

A married woman aged 42, without children, noticed a lump in the right breast in November, 1946. This was removed elsewhere in February, 1948, and histological examination showed a carcinoma. A week later I performed a right radical mastectomy. In May, 1949, radiological examination showed metastases in the ribs, pelvic bones, right femur, and probably in the neck of the left femur. Palliative high-voltage x-irradiation was given to relieve the pain they were causing, and she was also given methyltestosterone, 50 mg. daily, until September, 1950. There was marked reduction in the pain in the right hip and improvement in the pain in her back. In March, 1951, she looked and felt very well; hot flushes occurred after the testosterone was withdrawn. Flexion was slightly limited at the right hip, otherwise movements in both hips were full. Testosterone therapy was recommenced and the dose increased to 75 mg. daily by April, 1952; it was withdrawn in May, 1952. At this time palliative x-irradiation was given to the right hip. In June, 1952, pain occurred in the right shoulder and there was radiological evidence of a metastasis in the upper part of the shaft of the right humerus; palliative x-irradiation was given to this region.

On October 20, 1953, methyltestosterone, 25 mg. daily, was given because radiological examination of the pelvic bones showed that the affected areas were bigger and an increase had occurred in the area of rarefaction in the right

humerus. I examined the patient on December 22 and found her in excellent health and living a normal life; there was no evidence of soft-tissue metastases; the radiological appearances of the osseous metastases persist. There is very little hair on the face; her voice has a lower pitch than normal.

Case 3

A married woman aged 60, with one child, noticed a lump in the left breast in November, 1951, and in February, 1952, a left radical mastectomy was performed elsewhere for a carcinoma, and followed by a course of high-voltage x-irradiation.

She was brought to hospital by ambulance on December 16, 1952. On examination she looked ill, cyanosed, and dyspnoeic. There were no clinical signs of local recurrence; metastases in the chest were suspected. Radiological examination of the chest showed some elevation of the left diaphragm, the trachea was displaced to the left, and there were enlarged hilar shadows on both sides and an opacity in the left upper zone of the lung which resembled lymphogenous spread of carcinoma. The patient was treated with testosterone phenylpropionate, 50 mg. twice weekly. Examination on March 24, 1953, showed that she had improved and was gaining weight. The testosterone injections were increased to 100 mg. twice a week. On June 23, the improvement was maintained; her voice was lower in pitch, and the testosterone injections were decreased to 50 mg. twice weekly. On November 24 the patient stated that she felt well; the testosterone injections were continued, and thyroid extract, $\frac{1}{2}$ gr. (32 mg.) twice daily, was prescribed. A radiological examination of the chest showed that the opacity in the left mid-zone was more clearly defined. When examined on December 22 she looked well, no dyspnoea or cough was present, her general condition was good, and there was no evidence of soft-tissue metastases.

Case 4

A married woman aged 56 first attended hospital on August 14, 1941, with a rodent ulcer involving the external canthus of the right eye, which was treated with low-voltage x-irradiation. On October 21, 1952, she complained of a lump in the left breast, and on examination it was found that the nipple was retracted and a carcinoma was present in the upper and inner quadrant, attached to the skin and deep fascia. The left axillary nodes were palpable. Radiological examination showed metastases in several right lower ribs, in the bodies of the eleventh and twelfth dorsal and the lumbar vertebrae, and also in the neck of the left femur. Injections of testosterone phenylpropionate, 50 mg. weekly, were given for four months. In March, 1953, she complained of pain in the lumbar spine; the injections of testosterone were stopped and ethinyl oestradiol, 0.05 mg., was given twice daily. In May a palliative course of high-voltage x-irradiation to the lumbar spine was given and the ethinyl oestradiol was continued.

On October 13 the patient was examined; she had no pain in her back and only a small area of residual thickening remained in the left breast; no lymph nodes were palpable in the left axilla. Radiological examination showed extensive osseous metastases in the spine, pelvis, and neck of the left femur. A follow-up letter dated December 18 stated that her condition remained the same.

Case 5

A married woman aged 49, with two children, attended hospital in August, 1953, with multiple skin nodules of carcinoma; the first of these had appeared six months previously. Thirteen years ago a hysterectomy for a fibroid uterus and excision of the right ovary for a cystadenoma had been performed elsewhere. In 1947 a left radical mastectomy was performed elsewhere for a carcinoma of the breast, proved by microscopical examination, and in 1952 a right radical mastectomy was done elsewhere for a car-

cino-ma of the breast, proved by microscopical examination. A course of x-irradiation was given after each operation.

On examination irradiation changes were seen in the left supraclavicular region; there were multiple skin nodules over a wide area, including the right chest wall, left hypochondrium, left iliac fossa, and the right arm. Radiological examination of the dorsal spine showed no evidence of metastases. Injections of testosterone phenylpropionate, 50 mg. twice weekly, were given. Examination on October 27, 1953, showed considerable regression in the skin nodules.

Case 6

A married woman aged 80, without children, attended hospital in April, 1949, with a lump in the left breast which had been present for nine years. It had been increasing in size slowly and had bled during the past two months. Three months after the lump appeared in the breast another lump developed in the left axilla. On examination an ulcerating carcinoma 7.5 by 6 cm. occupied the inner half of the left breast attached to the chest wall, and the nipple was destroyed. A hard lymph node 1.5 cm. in diameter was present in the left axilla attached to the skin. Radiological examination of the chest showed no metastases. A course of high-voltage x-irradiation was given to the left breast, left axilla, and left supraclavicular regions. On September 16, 1952, the ulcerating carcinoma and axillary lymph node was still present and the patient was treated with stilboestrol (5 mg., thrice daily) until November 20, when vaginal bleeding occurred and the stilboestrol was withdrawn. By December 20 the ulcerating carcinoma had almost healed. On October 13, 1953, it was seen that the lesion had regressed considerably, was dry and practically healed, and no abnormality was present in the left axilla. From April 21 she has had ethinyl oestradiol, 0.05 mg. twice daily. On January 12, 1954, the lesion was flat and healed.

A summary of results in the above cases is given in the accompanying Table.

Results of Hormone Treatment in Disseminated Breast Cancer

Case	Variety of Disease	Treatment	Survival Period after First Treatment Given	Survival Period after Start of Hormone Treatment
1	Carcinoma breast; cervical and bilateral axillary lymph node metastases; multiple skin nodules	Oophorectomy; excision right axillary lymph nodes. Methyltestosterone	5½ years	5½ years
2	Carcinoma breast; multiple osseous metastases	Radical mastectomy. H.V.T. (palliative). Methyltestosterone	6 "	4½ "
3	Carcinoma breast; pulmonary metastases	Radical mastectomy. Post-op. H.V.T. Testosterone phenylpropionate	2 "	1 year
4	Carcinoma breast; multiple osseous metastases	Testosterone phenylpropionate. Ethinyl oestradiol. H.V.T. (palliative)	1½ "	1½ years
5	Carcinoma breasts rt. and lt.; multiple skin nodules	Radical mastectomy rt. and lt. Post-op. H.V.T. Testosterone phenylpropionate	7 "	2 months
6	Ulcerating carcinoma breast; axillary metastases	H.V.T. Stilboestrol	4½ "	1½ years

Discussion

Each patient received benefit from hormone therapy with androgens or oestrogens, and Cases 1 and 2 are of special interest because they are in excellent health 5½ and 4½ years respectively later. In the first patient there is no evidence of carcinoma; in the second there is radiological evidence of bone metastases, but this is not adversely affecting the

patient's health. The voices of both patients are lower in pitch, but there is no other evidence of masculinization. The amount of hair on the face in Case 1 has diminished considerably and she has a much more youthful appearance than before the oophorectomy. The other patients will be followed up for a longer period to assess the results. If patients are enabled to live on in comfort for several years in spite of persistent cancer the value of this treatment will be established, and it is likely that some method will be found to counteract any unpleasant side-effects which may occur.

Since Loeser (1940) suggested testosterone therapy for advanced breast carcinoma several reports have described the effects in soft and osseous tissue dissemination. Additional information is now required on survival periods after this treatment is begun. More than 50 years have gone since Beatson (1896, 1902) wrote of the beneficial effect of oophorectomy in some of these patients, and it has received sporadic attention to the present time. This operation is also being performed in the younger pre-menopausal group of patients after radical mastectomy, and it is necessary to evaluate the end-results after the lapse of an adequate follow-up period.

Regarding the dosage of testosterone, I usually give a big dose during the first course of treatment, which in one patient has extended for 18 months. A careful check is kept on the patient's general condition, including examinations of the blood urea and serum calcium. An important observation is the improvement which occurs after the cessation of hormone treatment, and it is suggested that these interruptions play an important part. When they have obtained the maximum benefit from oophorectomy and androgen therapy there are certain patients with severe pain from osseous metastases who may be helped further by adrenalectomy. The selection of patients for this final form of treatment must be done carefully, and at present it seems that the number suitable for it is small.

Summary

The results of hormone therapy in a group of patients with disseminated breast cancer are described and attention is called to two patients who are in excellent health 5½ and 4½ years later.

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The Minister of Health is to be asked to receive a deputation from the London County Council on the question of the extension of chiropody services provided by the Council under the National Health Service. In the county of London facilities are provided at the rate of 1.38 chiropodist sessions per 10,000 population, but there is no provision in the City of London and in 13 other metropolitan boroughs. The Health Committee of the Council states that the inadequate and unbalanced service is due to the diversity of the arrangements taken over in 1948. They regard chiropody as essentially a preventive service, which could do much to prevent the ill-health resulting from foot trouble, and urge that an extension of the service is a logical development of the functions of the local health authority under the N.H.S. Act. The approval of the Minister was sought for a long-term scheme of extension of the service as a whole by 34%, and a short-term scheme for an immediate extension of the service in those boroughs without any service at all at present. All the clinics would be in existing or projected health service premises. The Minister replied that while appreciating the Council's concern in the matter he did not feel able to approve either of the schemes. Accordingly he is to be asked to receive a deputation.

ACUTE POST-OPERATIVE LARYNGEAL OBSTRUCTION

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Though large series of post-anaesthetic conditions have been reported from time to time, we have found little reference to lesions of the upper respiratory tract. Obstructions of various bronchi by mucus plugs giving rise to segmental and sometimes massive collapse of the lung are well known, but the more serious obstruction at the larynx is notably absent from the literature. Four cases of this grave complication occurring after grafting operations in children are presented.

Case 1

A girl aged 3 years was admitted to the burns unit with a history of having fallen into boiling water six weeks previously. Her general condition was poor and she had obviously lost weight. On examination an extensive granulating area involving her abdomen, back, and both lower limbs was found.

On the afternoon of the third day a grafting operation was performed under general anaesthesia induced with cyclopropane and oxygen and maintained with methyl N-propyl ether ("neothyl") and oxygen. A No. 1 "flexo-metallic" endotracheal tube was passed without difficulty and the operation was uneventful, though the defect was not fully grafted owing to its extent.

Shortly before midnight on the same night very slight stridor was noted, but was not regarded as significant. Next morning the stridor was more pronounced and was accompanied by a moist cough, but there was no other evidence of laryngeal obstruction. Treatment consisted of steam tent, postural drainage, and systemic penicillin. At midday she vomited after a bout of coughing and the larynx went into spasm, but this subsided on careful toilet of the pharynx by suction. Some time after this episode her breathing became more laboured and there was indrawing of the supra-sternal notch. This became more pronounced during bouts of coughing in her effort to clear the air passages of a tenacious sputum. At 4.45 p.m. an acute airway obstruction developed, followed by cyanosis, coma, and convulsions. The latter was localized to the right side of the face and the left side of the body.

An emergency tracheotomy was performed and aspiration of the air passage carried out, with considerable improvement in her colour. On cutting down the dressings on her abdomen to ensure unrestricted respirations an acute dilatation of the stomach was uncovered. This was thought to be due to sucking air into the oesophagus during the airway obstruction, and was deflated with a stomach tube.

Her general condition was still very poor and severe convulsions continued. An intravenous drip was set up and the convulsions were controlled with gallamine triethiodide ("flaxedil"). An initial dosage of 12.5 mg. of gallamine followed by 7.5 mg. within a few minutes sufficed to control this attack. A dosage of 2.5 mg. half-hourly was maintained, but convulsions recurred eight hours later. These subsided only after the administration of 50 mg. of gallamine in divided doses, and 12.5 mg. was given on any