ADRENALECTOMY IN CANCER OF THE BREAST AND PROSTATE

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Introduction

'Hormones,' said Sir Walter Langdon Brown, 'are administered to credulous patients by even more credulous physicians.' They have in truth been prescribed for almost every disease, in many cases without any justification. In the treatment of cancer of the breast they are often given quite indiscriminately and when all else fails both the androgenic and oestrogenic hormones have even been prescribed together. It is therefore a bold surgeon who tries to explain any of the facts relating to hormones and cancer let alone the theories which sustain such facts. Yet records not only of individual patients but also of large series of cases are now quite numerous in which the giving or withdrawing of a hormone has had striking effects upon the course of malignant disease, usually when this has involved the breast or prostate but occasionally when the growth is in other situations or in one of the ductless glands themselves. Before the production of synthetic hormones it was naturally easier to 'withdraw' than to give a hormone and of the organs which could be conveniently removed the testicles and ovaries were the most accessible.

Castration in both sexes has long been known to have effects upon the prostate, uterus and breasts and such observations date from earlier than is generally supposed both in the clinical and experimental fields. Recently attention has been drawn to the facts relating to the patient who in 1896 consulted Mr. G. T. Beatson of Glasgow on account of an advanced and inoperable carcinoma of the breast. Bilateral oophorectomy produced astonishing improvement and Beatson himself had the foresight to observe 'We must look in the female to the ovaries as the seat of the exciting cause of cancer, certainly of the mammae.' Interest was thus aroused and the first series of 54 cases treated in such a fashion was published by Boyd in 1900. Other and larger numbers followed but rather strangely, since on the whole the reports were encouraging, by 1905 the method had fallen into disfavour.

On the experimental side one is reminded that

it is almost 40 years since Lathrop and Loeb (1916) showed that castration of mice at an early age reduced the incidence of mammary cancers. Although as is usual in these matters mice tend to behave more reasonably than men, or rather women, it also seems to be true, as observed by Herrell (1937) and confirmed by Dargent (1949), that a woman who has been castrated is less likely to get cancer of the breast than one who has not. The position may be expressed very simply, indeed much too simply, thus: since castration (which equals oestrogen withdrawal) may prevent the occurrence of cancer and may also cause regression when it has occurred, it might therefore be expected that giving androgens (which equals oestrogen antagonisation) might have the same sort of effect. And in some respects this is true.

It is indeed a fact that surgical castration may cause regression of certain primary tumours and their metastases by hormone deprivation and in the same way the administration of antagonistic hormones should have the same effect. Hormone deprivation or administration will, however, only cause retardation in the rate of the growth: it does not affect the eventual outcome. An admirable survey of androgen therapy in advanced mammary carcinoma was published by Galton in the *British Journal of Cancer* in 1950. Burrows and Horning (1952) state that to maintain experimental endocrine neoplasias it is necessary to have a continuous supply of hormone, though the amount itself may be very small. One may conclude, therefore, that certain tumours owe their continued existence in greater or lesser degree to the adequate supply of a hormone. They are, in fact, hormone dependent. However, it is not the purpose of this article to pursue this matter further, but to give some account of the place of adrenalectomy in the treatment of cancer of the prostate and breast.

Cancer of the Prostate

The prostate gland secretes an acid fluid containing a small amount of alkaline phosphatase and a relatively larger quantity of acid phosphatase.

The growth of cancer of the prostate, like that of

the normal gland, depends on the secretion of androgens. The greatest source of this is the testis. The tumour is hormone dependent and the more it corresponds to the normal structure of the gland the more it appears to be controlled by hormone influence. The growth of prostatic cancer can, therefore, be affected (1) by neutralising the androgens (oestrogen therapy) or (2) by removing the source of androgens (orchidectomy and adrenalectomy).

As already stated, it has been known for many years that orchidectomy causes considerable regression of prostatic cancers. Unfortunately, after a variable time, usually from one to five years, the growth again progresses. Oestrogens have a variety of functions in cancer of the prostate. They inhibit androgens directly, decrease the secretion of gonadotrophins by the pituitary gland and act directly on the malignant cells. They have no effect on the adrenal glands however, the remaining source of androgens. It is therefore a logical step to remove the adrenal glands when the disease is no longer under control.

Cancer of the Breast

The control of breast development is due to the complex action of a number of hormones, i.e. oestrogens and progesterone, which are the primary agents responsible for mammary growth. Oestrogens control the development of the nipple and the ducts and progesterone causes development of the glandular structure of the breast. The ovaries and the adrenal glands secrete both oestrogens and progesterone, probably under the influence of the anterior lobe of the pituitary gland. In pregnancy the placenta itself is an important organ of internal secretion and produces large quantities of both oestrogens and progesterone. In fact, it is probable that no oestrogens are produced by the ovaries in pregnancy and that the placenta is the only source of supply during this time.

Cancer may occur in the breast at any time after puberty. The rapidity of spread and the predilection of metastases for certain sites depend to a large extent on hormonal influence. An interesting tumour has been recorded by Foulds (1949). This is a mammary carcinoma occurring spontaneously in mice which appears during pregnancy and grows rapidly. In some cases it has been found that growth stops after pregnancy and does not recur unless another pregnancy supervenes.

In pregnancy, when there is maximal secretion of oestrogens and progesterones by the ductless glands and the placenta, it has long been recognised that cancer nearly always pursues a rapid and disastrous course. To a lesser extent, premenopausal cancer is more rapidly growing than when it

occurs later in life. There is some evidence that oestrogen production continues after the menopause and it is probable that there is still some remaining tissue in the post-menopausal ovary which remains sensitive to pituitary gonadotrophic hormones. Since castration may cause regression of both the primary tumour and of metastases it might be expected that androgens (in the form of testosterone) would inhibit the growth. Farrow and Woodard (1942) drew attention to the connection between ovarian activity and bone metastases commenting on a tendency for them to occur early in premenopausal women with cancer and late in the postmenopausal group. The effects of androgen therapy are surprisingly variable and inconstant. Paradoxes abound. On the whole testosterone benefits patients with skeletal metastases whilst stilboestrol quite unexpectedly often causes marked regression in soft tissue recurrence and, as had recently been confirmed by Stoll and Ellis (1953), in pulmonary metastases as well. There does not seem to be an adequate explanation for this effect apart from the theory that an excess of oestrogens inhibits the gonadotrophic hormones of the pituitary gland while the ovaries and adrenals 'atrophy,' with the result that this causes considerable fall in endogenous oestrogens. The same effect is produced by the administration of A.C.T.H., which rapidly results in adrenal cortical atrophy. Similarly the repeated injection of insulin in the experimental animal causes pancreatic atrophy.

There is evidence, therefore that the growth of well differentiated mammary cancer may be controlled (1) by removal of oestrogens and progesterone (ovariectomy, adrenalectomy and removal of placenta by immediate termination of pregnancy), (2) by 'neutralisation' of oestrogens (by testosterone); or (3) by stilboestrol.

The Adrenal Gland

The adrenal gland is made up of two distinct organs, the medulla and the cortex. The medulla consists of irregularly arranged polyhedral cells containing granules of adrenalin and nor-adrenalin. From the cortex two physiologically active substances can be obtained, a crystalline component and the amorphous fraction. The crystalline component consists of a steroid which can be divided into three main groups: (1) Oxycorticoids, i.e. corticosterone and cortisone. These correct the metabolism of carbohydrates, fats and proteins. (2) Desoxycorticoids (Doca). This acts by restoring the normal ionic balance. (3) Sex hormones; progesterone, oestrogens and androgens. The amorphous fraction is of unknown composition but is 98 per cent. of the adrenal cortical secretion and maintains life in adrenalectomised

animals, even when administered in very small quantities. Gonadectomy alone does not by any means cause complete elimination of urinary androgens and oestrogens.

Huggins and Hodges showed in 1941 that 70 per cent. of prostatic cancers regressed after castration and they demonstrated a similar effect from the administration of oestrogens which at that time had recently been synthesised. It was also recognised that castration stimulated the anterior lobe of the pituitary gland and produced adrenal cortical hyperplasia. This led Huggins and Scott in 1945 to suggest that the relapses during treatment with stilboestrol of patients with carcinoma of the prostate might be due to an increase in the androgen output of the adrenals. Bilateral total adrenalectomy was performed upon four men with advanced disease but owing to the difficulties of substitution therapy none survived very long. No mention is made of any improvement in the course of the disease. Since the discovery of cortisone it has been possible to remove both glands and to keep the patient in complete health on a maintenance dose by mouth of less than 50 mg. of cortisone daily. The dependence for survival upon cortisone is no worse than that of the diabetic patient upon insulin or the myxoedematous patient upon thyroxine.

Bilateral Adrenalectomy

Preparation of the patient. This does not differ from that which precedes any other major abdominal operation apart from the cortisone replacement. Often of course patients with advanced malignant disease and widespread deposits are 'poor risks' and such measures as are necessary or possible to improve the general condition are undertaken. On the day before the operation 200 mg. of cortisone, 10 mg. of desoxycorticosterone acetate and 5 g. of sodium chloride are given, the first two intramuscularly, the last by mouth. The accompanying table shows the amounts of these three substances which are needed on the day before and the days following the operation: O indicates the operation day.

O minus 1

Cortisone (intramuscular) 50 mg. 4 times (6 a.m., noon, 6 p.m. and midnight).

Desoxycorticosterone acetate (intramuscular) 5 mg. once (6 a.m.).

Sodium Chloride (oral) 5 g. once (6 p.m.).

Operation: 9 a.m.

Cortisone (intramuscular) 150 mg. (8 a.m.).

Desoxycorticosterone acetate (intramuscular) 5 mg. (8 a.m.).

Cortisone 50 mg. 4-hourly (post-operatively).

O plus 1

Cortisone (intramuscular) 50 mg. 4 times.

Desoxycorticosterone acetate (intramuscular) mg. once.

Sodium Chloride (oral) 3 g. once.

O plus 2

Cortisone (intramuscular) 50 mg. twice.

Desoxycorticosterone acetate (intramuscular) 0.3 mg. as indicated.

Sodium Chloride (oral) 3 g. once.

The operation. Experience has shown that this presents only two problems. The first is access, the second is the isolation and ligature of the adrenal vein, the only vessel of any importance. It is generally agreed that the best approach is gained by resecting as much of the 12th rib as possible and this entails division of some of the lateral fibres of the sacrospinalis muscle. After sub-periosteal removal of the rib the pleura is identified and stripped upwards and the perirenal fascia incised. The upper pole of the kidney may or may not be seen but the adrenal gland is fairly easily recognised both by palpation and by its characteristic appearance, the fine lobulation and deep golden colour being quite distinct from the surrounding fat. The gland is mobilised by dividing numerous strands of nerve fibres enclosing it until on the peritoneal aspect the adrenal vein is seen. The vein drains to the inferior vena cava on the right side and to the renal vein on the left. Both veins are rather short and 'stubby' and are best ligatured by means of a thread carried in an aneurysm needle, as near the gland as possible. The arterial supply and any smaller veins are sealed with the diathermy. The gland, grasped in tissue forceps, is then gradually dissected out. In the majority of cases this is a straightforward procedure but metastatic deposits may cause adherence to surrounding structures. Anatomical abnormalities such as inclusion of the gland in the upper pole of the kidney or close adherence to the bare area of the liver on the right side may cause some difficulty in mobilisation.

If both adrenal glands are being removed at the same operation the prone position is adopted, the table being 'broken' slightly or a pillow being placed under the abdomen. Two surgeons may operate together without unduly impeding each other and by doing so considerably reduce the length of the operation. If it is decided to combine bilateral ovariectomy or orchidectomy with the removal of only one adrenal the patient is turned on the side to the conventional 'kidney position' after sewing up the laparotomy incision or the two scrotal incisions as the case may be. The 12th rib is then removed to expose the gland in the manner already described. The second gland is removed two weeks later. It has been found that division of some of the fibres of both sacrospinalis muscle

The following table gives details of the patients treated.

Case No.	Diagnosis	Age	Indication for Operation	Pain	Relief of Pain	Survival	Regression	
							of Primary (if still present)	of Metastases
1	Carcinoma Breast	48	Pulmonary metastases	O	—	Died 5 weeks	—	No change
2	Carcinoma Breast	70	Multiple bony metastases	+++	Much improved	Died 5 weeks	—	No change
3	Carcinoma Breast	51	Multiple bony metastases	+++	Less pain and improved walking	Alive 6 mths.	—	Slight
4	Carcinoma Breast	36	Multiple bony metastases	++	No change	Died 3 mths.	Slight	No change
5	Carcinoma Breast	50	One metastasis lumbar spine	++	Much improved	Alive 6 mths.	—	Definite
6	Carcinoma Breast	51	Metastases in choroid and bones	++	Much improved	Alive 7 mths.	—	Definite
7	Carcinoma Prostate	61	Multiple bony metastases	++	Complete relief	Alive 6 mths.	—	No change
8	Carcinoma Breast	60	Multiple bony metastases	++	Complete relief	Alive 3 mths.	No change	Increased
9	Carcinoma Breast	45	Multiple bony metastases	++	Much improved	Alive 2 mths.	—	No change
10	Carcinoma Breast	40	Multiple bony metastases	+++	Improved	Alive 2 mths.	—	No change
11	Carcinoma Breast	39	Multiple bony metastases	+++	Much improved	Alive 2 mths.	—	Increased
12	Carcinoma Breast	67	Stage III. Huge primary No metastases	O	—	Alive 1 mth.	Definite	—
13	Carcinoma Breast	60	Pulmonary metastases	O	—	Alive 1 mth.	—	Definite
14	Carcinoma Breast	49	Vast skin ulceration. Pulmonary metastases	+	Died 12 hours after 1st stage		—	—
15	Carcinoma Breast	45	Multiple bony metastases	+++	Complete relief	Alive 4 mths.	—	No change
16	Carcinoma Breast	70	Multiple bony metastases	+++	Much improved	Alive 11 mths.	Very marked	Doubtful
17	Carcinoma Prostate	56	Multiple bony metastases	+++	Much improved	Died 2 mths.	—	No change
18	Carcinoma Breast	39	Multiple metastases	+++	Improved	Died 2 mths.	—	No change
19	Carcinoma Breast	38	Multiple metastases	++	Improved	Died 3 mths.	—	No change
20	Carcinoma Breast	39	Multiple metastases	++	Improved	Alive 3 mths.	—	No change

does not prevent the patient from being ambulant 24 to 48 hours after the operation.

Post-operative treatment. The table shows the amounts of cortisone, desoxycorticosterone acetate and salt which it is necessary to give for the first two days. During this period it is essential to keep a careful watch upon the blood pressure and the systolic pressure should be kept in the region of 100 mm. of mercury by adjusting the rate of an intravenous drip of 1:1000 nor-adrenaline in saline. Not more than 1500 ml. of fluid should be given each 24 hours and in order to keep an accurate measurement of fluid intake and output an indwelling catheter should be kept in the bladder for the first three days. Subsequent to the second post-operative day the dosage of both steroids is gradually reduced until the sustaining dose of cortisone alone, 25-50 mg. by mouth, is reached about a week after operation.

Results

Adrenalectomised patients are not in any way incapacitated. Very little supervision is needed as the maintenance dose of cortisone is adequate for all ordinary conditions of life. Most patients take their tablets in the morning and in the evening.

Twenty patients with extensive metastases causing intractable pain have been subjected to operation by us. There has been no selection of cases, the presence of severe pain being the criterion for operation. There has been one immediate post-operative death. The uncomplicated post-operative course in the really ill patient has been most gratifying and especially the improvement in the general condition and well-being of the patient. The blood pressure has invariably fallen, systolic by 20-40 mm. and diastolic by rather less, following the operation, but it has been found in those patients who have survived more than three months that the pressure gradually returns to pre-operative levels. It is too early to speak of survival periods for this is not intended as anything more than a palliative procedure. Nevertheless, it is noteworthy that five patients are alive and symptom-free six to eleven months post-operatively. More important, only one patient failed to get relief from pain.

Summary

Apart from X-ray therapy to individual deposits, morphia and other analgesics, and operations such as leucotomy there has previously been no treat-

ment for patients with carcinoma of the breast and prostate who suffer extreme pain from metastases in bone. But relief of pain can now be assured in the majority of cases by bilateral adrenalectomy. Regression of the primary tumour occurs much less frequently than that of the metastases.

Bilateral adrenalectomy is a practical proposition and no undue hardship is imposed upon the adrenalectomised patient.

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THROMBOSIS OF THE INTERNAL CAROTID ARTERY

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Numerous are the instances in the annals of medicine of discoveries made and subsequently forgotten, but this cycle seems to have recurred several times before angiography of the carotid artery revealed anew the frequency and the complications of occlusion of the internal carotid artery. The reasons for this recurring oblivion were twofold:

1. Examination of carotids in the upper part of the neck and carotid canals is not usually performed in routine autopsy.

2. Ramsay Hunt in 1914 gave the other reason for the neglect of this subject as follows: 'The assumption that the circle of Willis is sufficient to carry the blood into an obstructed vascular area when such obstruction is situated below the level of the anterior and posterior communicating arteries.'¹

This assumption was not only based on anatomical grounds but also on the experience of the effects of ligaturing these arteries. This operation was frequently performed during the 19th century for a variety of 'nervous disorders' such as epilepsy and trigeminal neuralgia, as is testified by the publication of four large series of cases collected during the second half of the century and quoted by Ramsay Hunt. In only 16 per cent. of some 1,200 cases comprising a variety of conditions did cerebrovascular accidents supervene—and this before the days of asepsis!

The present revival of interest in the subject of carotid thrombosis began after cerebral angio-

graphy came into wide use, and confirmed Ramsay Hunt's contention that occlusion of carotid arteries was not uncommon.

Pathology

Frequency. On combining the three large published series of unselected post-mortem examinations, which included a routine inspection of the carotid arteries in their entirety, the incidence of macroscopically visible thrombosis and embolism of this artery can be said to be approximately 1.6 per cent.^{2, 3, 4} The incidence will to some extent vary in accordance with the average age of the autopsy material.

The following classification of the various conditions causing occlusion of the carotid artery either by thrombosis or embolism has been suggested by Hultquist:

1. Trauma.
2. Morbid processes affecting the tissues in the immediate relation of the carotid arteries.
3. Cardiovascular diseases.

1. Trauma

Non-penetrating injuries to the neck may occasionally be followed within 6 to 48 hours by rapid onset of hemiplegia due to spreading thrombosis of the internal carotid artery. This was described by Northcroft and Morgan, and more recently the subject was reviewed by Schneider and Lemmen.^{5, 6} Cases of this nature simulate extradural and subdural haematomas, as is illus-