

RES MEDICA

Journal of the Royal Medical Society



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Abstract

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Reporting his findings to the Medico-Chirurgical Society of Edinburgh, Beatson summed up:

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ISSN: 2051-7580 (Online) ISSN: 0482-3206 (Print)

Res Medica is published by the Royal Medical Society, 5/5 Bristo Square, Edinburgh, EH8 9AL

Res Medica, April 1967, 5(4): 19-21, 23-25

doi: [10.2218/resmedica.v5i4.505](https://doi.org/10.2218/resmedica.v5i4.505)

ENDOCRINE ASPECTS OF BREAST CANCER

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INTRODUCTION

A relationship between the endocrine system and breast cancer was first demonstrated by Beatson in 1896, when he obtained some benefit from oophorectomy in two patients with advanced disease. Until that time the treatment of breast cancer was limited to removal of the mamma and excision of superficial metastatic or recurrent nodules. The practice of castrating cows to maintain lactation after calving suggested to Beatson that the ovaries must be concerned in some way with the regulation of the physiological processes of the breast.

Reporting his findings to the Medico-Chirurgical Society of Edinburgh, Beatson summed up :

"The conclusion I draw from two cases I have brought under notice is this — that we must look in the female to the ovaries as the seat of the exciting cause of carcinoma, certainly of the mamma"

He further emphasised :

1. "That there seems to be evidence of the ovaries and testicles having control in the human body over local proliferation of epithelium".
2. "That the removal of the tubes and ovaries has effect on the local proliferation of epithelium which occurs in carcinoma of the mamma"

3. "That the effect is best seen in cases of carcinoma in young people, a class of case where local removal of the disease is often unsatisfactory."

Within the next decade, Boyd (1900) and Lett (1905) confirmed Beatson's observations and showed that about one-third of patients responded favourably to oophorectomy. It is interesting that no improvement in this figure has taken place since then, for the Joint Committee of the American Medical Association on Ablative Procedures in Breast Cancer reported that objective tumour regression occurred in 29% of women castrated before or during the menopause (Taylor, 1962).

In the seventy years since Beatson's pioneer effort the concept of hormone-dependence has become an accepted biological characteristic of certain tumours, particularly of the breast and prostate. It had its origin in the classical observations of Huggins and his colleagues who demonstrated that in dogs not only are the physiological processes of the prostate under endocrine control but that tumours of the glands regress after castration or in response to the administration of oestrogens (Huggins and Clark, 1940). It was subsequently shown that cancer of the human prostate could be influenced in a similar way.

The development of our understanding, albeit imperfect, of the relationship between endocrine status and breast cancer is the result

of a fruitful alliance of clinical practice, biochemical investigation and animal experiment. Some of the most significant contributions in these fields are discussed below.

EXPERIMENTAL TUMOURS IN ANIMALS

A great deal of research has been carried out on experimental tumours, particularly in the United States and a voluminous literature has accumulated. Three main lines of investigation have been followed.

1. Induction of tumours by hormones

Only three years after Doisy had isolated the first crystalline oestrogen, Lacassagne (1932) induced mammary cancer in male mice by repeated injections of the hormone. Many workers since have confirmed that oestrogens may promote tumour growth in several species (Noble, 1957).

The breast is not the only organ to be affected. Oestrogen administration has yielded lymphoid tumours in mice, chromophobe tumours of the anterior pituitary, fibromyomata of the uterus in guinea pigs, malignant tumours of the cervix uteri, malignant renal tumours in male golden hamsters and interstitial cell tumours of testes in mice.

Although oestrogens are the most potent, other hormones have been found also to induce tumours. Moon and his colleagues (1950), for example, described lymphosarcomata, adrenal cortical and ovarian tumours in rats receiving injections of pituitary growth hormone.

These examples demonstrate the carcinogenic effects of the administration of exogenous hormones. The secretion of endogenous hormones may be altered by suitable manipulation of the endocrine system. Elegant experiments which demonstrate the interdependence of endocrine organs, and the oncogenic potential of interference with the feed-back mechanisms were reported by Biskind and Biskind (1944). They excised both ovaries from rats and transplanted one of them into the spleen. Ovarian oestrogen was thus liberated directly into the portal circulation and inactivated by the liver. They concluded that the resultant excessive production of anterior pituitary gonadotrophins was responsible for the granulosa-cell tumours and luteomata in the transplanted ovary.

2. The effects of hormones on spontaneous mammary tumours

Spontaneous fibroadenomata occur in about fifty per cent of elderly female rats of the

Sprague-Dawley strain. These tumours are readily transplanted into young rats and their experimental value depends upon their responsiveness to alterations in the animal's endocrine environment.

A biphasic effect on the growth of the tumour has been observed during the administration of oestrogen both in intact (Miller and Noble, 1954) and ovariectomised rats (Huggins, et al., 1956). Small doses of oestrogen promote, and large doses inhibit, the growth of the tumours. The effects of androgenic steroids have also been intensively investigated by Huggins and Mainzer (1957) and in general, they are inhibitory.

3. Endocrine factors influencing hydrocarbon-induced mammary cancers

The two most useful mammary carcinogens are 3-Methylcholanthrene and 9, 10-Dimethyl-1, 2-Benzanthracene (DMBA). The tumours appear within a few weeks in response to a single intragastric instillation or intravenous injection (Huggins, Briziarelli and Sutton, 1959). They are adenocarcinomas histologically similar to human tumours. They are also hormone-dependent, and regression or disappearance of the tumours occurs after oophorectomy, after hypophysectomy and in response to the exhibition of exogenous steroids.

On the basis of their growth characteristics the tumours can be classified into three biological types. Some grow to a certain size, then regress spontaneously; some remain static after an initial period of growth; and others continue to enlarge throughout their life-history (Young, et al, 1963).

Many of these features are characteristic of the human disease, and the hydrocarbon-induced mammary tumour is, therefore, a unique experimental model for intensive investigation of the endocrine factors concerned in the induction and maintenance of breast cancer.

CLINICAL OBSERVATIONS

In clinical practice, alteration of the endocrine state of patients has been achieved either by the administration of steroid hormones or by ablation of endocrine organs. Such measures have generally been limited to the treatment of advanced malignant disease.

Endocrine Ablative Procedures

1. Oophorectomy

Since Beatson's original observations there have been many confirmatory reports of the value in certain cases of removal of the ovaries.

Elimination of ovarian function has also been achieved by radiotherapy, and Douglas (1952) reported a favourable response in 20 per cent of patients with advanced disease. A major debate has now centred on the timing of castration, which may be done either as a prophylactic measure at an early stage in the disease or deferred until metastases have appeared. From an extensive review of the relevant literature Lewison (1962) concluded that therapeutic oophorectomy is an effective palliative procedure in about 25 per cent of patients and that there is a well defined trend towards prolonged life expectancy and improved survival rate from prophylactic castration whether achieved by surgery or by irradiation.

Oophorectomy is occasionally necessary in young women for the treatment of gynaecological disorders. Careful follow-up studies (Lilienfield, 1956; Hirayama and Wynder, 1962) indicate that in these women there is a reduced incidence of breast cancer in later years, particularly if the operation was done before the age of 37 years. Bilateral oophorectomy offers the greater protection, but even women who have had one ovary excised are significantly less prone to the subsequent development of cancer. These reports suggest that the ovary and its secretions are important in the induction as well as the maintenance of human breast cancer.

2. Adrenalectomy

Removal of the adrenal glands is designed to remove the main source of extra-ovarian sex hormones. It is usually combined with oophorectomy even in post-menopausal women in whom secretion of ovarian hormones continues although the uterus atrophies.

In 1945 Huggins and Scott obtained tumour remission following bilateral adrenalectomy in a man with advanced prostatic cancer. Survival lasted only four months in spite of the administration of deoxycorticosterone and a high salt intake. By 1952 cortisone was readily available and Huggins and Bergenstal successfully operated on seven patients with breast cancer of whom three, including one man, responded favourably. Since this time, many reports have indicated a variable degree of success, but remission occurs in about one-third of patients who are submitted to adrenalectomy and oophorectomy.

3. Hypophysectomy

This operation was introduced by Luft and Olivecrona in 1953. They reported (1958) a total remission rate of 44 per cent — regression of tumour in 29 per cent, and arrest of disease in 15 per cent of patients. A comprehensive survey of the value of adrenalectomy and hypophysectomy has been conducted by the Joint Committee of the American Medical Association (1961). The results from twelve American Clinics (representing a total of 673 patients) demonstrate no difference between the two methods; there was a 31 per cent response in each.

Administration of Hormones

1. Oestrogens

The isolation of a crystalline oestrogenic hormone by Doisy in 1929 heralded an explosive development of steroid biochemistry, leading eventually to the elaboration of synthetic oestrogens. The value of these compounds in the treatment of advanced malignant disease was demonstrated by Haddow, Watkinson and Paterson (1944). Perhaps the most significant feature of these studies for the clinician is that for the first time, they enabled him to write a prescription for the treatment of cancer. This marks the origin of chemotherapy in malignant disease.

Oestrogen therapy is of greatest value in post-menopausal women in whom tumour regression occurs in about 35 per cent with a mean survival time of 27 months compared with 10 months in non-responsive patients (Council on Drugs of the American Medical Association, 1960).

2. Androgens

Loesser first demonstrated in 1939 that between 20 per cent and 25 per cent of patients respond to androgen administration, irrespective of menopausal state. Survival times recorded by the Council on Drugs (1960) were 19 months and less than 10 months in responsive and non-responsive patients respectively. Hirsutism, acne, deepening of the voice and increase in libido are displeasing side-effects which have dissuaded many clinicians, and patients from continuing treatment. Numerous steroid derivatives have been investigated by the Co-operative Breast Cancer Group (1964) in an attempt to find compounds which are non-virilising and yet retain their therapeutic effectiveness. Although some success has been achieved it is doubtful whether these compounds are as effective as esters of the naturally occurring androgens.

3. Other Hormones

High doses of corticosteroids are beneficial in castrated patients and are believed to act by inhibition of the adrenal cortex and consequent reduced production of oestrogen. Prednisolone, a synthetic corticosteroid, is more effective than cortisone and causes less water retention.

Progesterone appears to have little effect but a synthetic progestational compound, 9 α -bromo-11-ketoprogesterone, studied by Goldenberg and Hayes (1959) produced a 20 per cent remission. Combinations of oestrogen and progesterone may be more effective. Stimulated by the observation that hydrocarbon-induced experimental tumours responded to administration of high doses of oestradiol and progesterone, Landau and his colleagues (1962) tried the combination in 15 patients, of whom 9 responded though only for a short time. Recently, Stoll (1967) has reported a 20 per cent response in patients receiving the oral contraceptive, Lyndiol, in which an oestrogen and progestin are combined.

Effectiveness of Treatment

It is evident from this brief outline that about one-third of patients respond to the administration of hormones or to endocrine ablative procedures. Adverse reactions to treatment do occur, however. Wilson, Jessiman and Moore (1958) have noted exacerbation of metastatic disease following oophorectomy and adrenalectomy, and Cade (1958) has reported similar effects from the administration of androgens and oestrogens. The results in human patients prompt comparison with the biphasic effects of oestrogens and androgens observed in experimental tumours, and emphasise our present ignorance of the fundamental relationships between hormones and growth.

Much has been written and many opinions have been expressed on the value of certain clinical criteria for the selection of patients with metastatic disease for major endocrine surgery. In his comprehensive review of this subject Fairgrieve (1966) concludes that two categories of patient are most likely to benefit; those with a long "free-interval", that is, in whom more than a year has elapsed between primary treatment and first recurrence, and those with skeletal or skin metastases. He emphasises the importance of assessing the extent and type of metastases. Slowly growing cutaneous or lymph node recurrences are perhaps best treated by local surgery or radiotherapy. Major surgery is inappropriate in pre-terminal states when life expectancy is limited.

Between these two extremes are patients with metastatic disease which is progressive and/or symptomatic for whom endocrine ablative procedures should be reserved.

The main problem which besets the clinician is his inability to forecast for the individual patient whether or not a favourable response will be obtained. It is towards this end that the greatest efforts have been made in the last decade.

BIOCHEMICAL INVESTIGATIONS

One of the most rewarding features of medical practice in recent years has been an awareness of the need for collaborative efforts by members of different disciplines, especially in assessing complex biological problems. Not least successful among the alliances so established has been the team comprising endocrinologist, biochemist, surgeon and radiotherapist. Much pioneer work along these lines has been actively pursued in Edinburgh.

The principal approach of the steroid biochemist has been the determination of steroid metabolites in urine and their relationship to clinical observations.

Urinary Oestrogens

Animal experiment and clinical observation indicated that oestrogen played a major role in the induction and maintenance of breast cancer. The elaboration of reliable methods for the analysis of urinary oestrogens (Brown, 1955 and Bauld, 1956) provided the means for intensive collaborative activity in Edinburgh. Strong and his colleagues (1956) found no correlation between pre-treatment oestrogen levels and subsequent response to the administration of stilboestrol or endocrine ablative operations. Subsequent reports from other centres have confirmed these observations.

Attempts to correlate the clinical result with changes in urinary oestrogen levels occurring after ablative procedures similarly have been disappointing. Some patients improve in spite of continuing high levels of urinary oestrogen and others deteriorate when oestrogen excretion has fallen to negligible amounts (Brown, *et al.*, 1959).

Several studies have indicated, however, that post-menopausal women with breast cancer differ from the normal population by an increased excretion of oestrogen. The physiological significance of this finding remains obscure, and more detailed study is required to establish its possible relationship to the development of breast cancer.

Overall, the efforts to relate oestrogen excretion to the course and prognosis of human breast cancer have been inconclusive.

Urinary Androgens and Corticosteroids

The estimation of urinary androgen and corticosteroid metabolites has proved the most hopeful approach so far. A major contribution in this field has resulted from the collaborative studies in London by Guy's Hospital and the Imperial Cancer Research Fund. Workers there have investigated patients with advanced disease, patients with early breast cancer and normal women.

1. Advanced breast cancer

Urine was collected before operation from patients treated by adrenalectomy or hypophysectomy and estimations were made of gonadotrophins, androgen, oestrogen, corticosteroids and progesterone metabolites. By retrospective analysis of the data it was found that patients who responded satisfactorily to the operation were characterised by a relatively low excretion of corticosteroids and relatively high levels of urinary androgens. A reasonable distinction between the responsive and unresponsive clinical groups was obtained by expressing 17-hydroxy corticosteroids (17-OHCS) and 11-deoxy-17-oxosteroids as a simple ratio.

A more sophisticated statistical approach led to the formulation of a discriminant function which takes the form

$$80-80 [17\text{-OHCS (mgm/24 hrs.)}] + \text{aetiocholanolone}^* (\mu\text{gs/24 hrs.})$$

The design of the formula is such that a negative or positive number is obtained depending on the relative values of the steroids. By this means a clearer distinction between the clinical groups was obtained. A significant majority of patients with a "positive discriminant" responded to adrenalectomy or hypophysectomy whereas the results of treatment in the "negative discriminant" category were generally poor (Bulbrook, *et al.*, 1962).

When the discriminant function is considered in association with clinical observations a group of poor-risk patients with advanced disease is revealed. Remission is obtained in only 2 per cent of "discriminant-negative" patients in whom the primary tumour was noted within six years after the menopause and in whom recurrence had appeared within two years of primary treatment.

2. Early breast cancer

There are indications that the relationships originally demonstrated in advanced breast

*Aetiocholanolone is one of the urinary androgen excretion products.

cancer also obtain at an early stage of the disease. A negative discriminant function is a rare finding in normal women under the age of 60 years but has been observed in about 50 per cent of patients with early breast cancer. In these patients the incidence of recurrence is four times higher and the death rate is eight times greater than those with a positive discriminant (Bulbrook, *et al.*, 1964).

3. Prospective studies on normal women

The preceding observations suggest that in some women with breast cancer there is an abnormality in the secretion of androgens and corticosteroids. Prognosis is poor in these patients, perhaps because the tumour has become hormone-independent. To determine whether the abnormality precedes the development of disease or results from the presence of the tumour a prospective survey was set up in Guernsey in 1961.

Almost 5,000 healthy female volunteers from this relatively closed population have provided one complete collection of urine. To date, breast cancer has developed in nineteen of the women. Analysis of the results suggests that the excretion of androgen and corticosteroid metabolites was abnormal in a significant proportion of the patients prior to the development of the disease (Bulbrook and Hayward, 1967).

CONCLUSION

The management of breast cancer presents a formidable challenge to the clinician. Intensive research on the relationship of the endocrine system to the induction and maintenance of mammary tumours has provided some insight into the nature of the disease. Some tumours appear to regress after alteration of the hormonal environment in which they have developed, others do not. It is not yet possible to determine the biological nature of a particular tumour at a sufficiently early stage in the disease to orientate the search for effective counter-measures. There are indications however, that poor-risk patients, and even healthy women who are "susceptible" to the disease, might be identified by abnormalities of secretion of urinary steroids. It should be possible in the future to confirm these suggestions and to simplify the measurements so that they are more generally available. Thereafter, attempts to produce a more favourable endocrine environment might not only be possible, but acceptable in a society in which hormonal modifications for fertility and birth control are now commonplace.

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A Case For Dissection

In an anonymous monograph in the Library entitled "An Answer to the Several Attacks which have appeared against the University of Edinburgh" the author includes in his refutation of the "calumnies which have been circulated against this University, particularly that lately published in the city of Dublin" an interesting little snippet on Edinburgh dissecting habits in the early 19th century:

"Let us figure to ourselves a group of students assembled round a subject. One is cutting out an eye, another is making a prize of the heart, which he is proceeding to examine at his leisure, a third is grubbing in the entrails, and a fourth practising the insertion of the female catheter; the whole party brandishing their scalpels, singing and laughing, as merry as cobblers (sic) over their awls. Suppose that the lecturer were to come in and to recognise in this one-eyed, mangled, heartless creature, the frail remains of the wife of his bosom, the sister, or daughter, whom he had cherished with the tenderest affection! How would he be able to bear such a sight? Would he not start back with horror? Would it not put all his philosophy at once to flight?"

Perhaps they weren't calumnies after all . . .