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ADRENALECTOMY FOR BREAST CANCER*

BY

Sir STANFORD CADE, K.B.E., C.B., F.R.C.S., F.R.C.O.G., M.R.C.P.

Senior Surgeon, Westminster Hospital

It is now recognized that cancer of the breast and prostate are hormone-dependent tumours—that is, cancers which can be controlled by the administration of sex hormones. That removal of the ovaries influences advanced breast cancer has been known since 1896, when George Beatson published the first reports on this method of treatment. By 1905 Hugh Lett had reported 99 cases of oophorectomy for the late stages of mammary carcinoma. The popularity of this operation waxed and waned during the following half-century owing to the development of radiation-induced menopause. To-day it is thought by many that radiation menopause is not equivalent to surgical castration and that it does not abolish oestrogen formation. Huggins and Bergenstal (1951, 1952) demonstrated that the adrenal cortical hormones sustain mammary cancer and that their withdrawal is followed in a number of cases by marked regression of the tumour. Prolonged survival of adrenalectomized patients on cortisone maintenance has given a great impetus to this method of treatment (West *et al.*, 1952; Taylor *et al.*, 1953; Pyrah and Smiddy, 1954).

Huggins has drawn attention to the following important observations: (1) Gonadectomy is followed by a compensatory hypertrophy of the adrenals and by increased cortical function. (2) In men, removal of the testis is followed by an increase of 17-ketosteroids in the urine, and these high values are eliminated by bilateral adrenalectomy. (3) Following oophorectomy, women continue to excrete oestrogens in the urine, but these compounds disappear from the urine after adrenalectomy. Further, Huggins and Dao (1953) formed the opinion that in a number of post-menopausal women the ovaries continue to have an active endocrine function, which indicates oophorectomy even after the menopause.

The rationale of bilateral oophorectomy and adrenalectomy is therefore the elimination of all known sources of hormones which can influence the growth of mammary cancer and the creation of a physiological environment poor in steroids.

The Natural Course of Breast Cancer

Mammary cancer varies in its rate of growth and power of dissemination from the slow and apparently harmless course of the "atrophic scirrhus" on the one hand to the rapidly fatal course of the "acute inflamma-

tory" type on the other. The variation noted in different histological types, in different age groups, in different hormonal states (pre- and post-menopausal and in pregnancy and lactation) indicates that the hormonal influence is variable and that some tumours are hormone-dependent to a greater degree than others and that some are independent of hormones. But in nearly all cases after a variable period of quiescence and localization the disease spreads locally, to the regional lymph nodes, to the skeleton, and to the viscera.

The early and localized stage of the disease can be controlled by surgical treatment; moderate extension can be alleviated by radiotherapy; in the early stages of dissemination the use of androgens or oestrogens may arrest the spread of the disease for variable periods. Bilateral adrenalectomy is indicated when the disease is disseminated and no longer amenable to treatment by surgical, radiological, and hormonal means. It is therefore a most important advance in the treatment of cancer of the breast and should be considered in patients in whom the disease is no longer amenable to the established methods of treatment.

This report is based on the experience of 69 bilateral adrenalectomies, 56 of these in advanced and disseminated breast cancer. The study of these patients has shown that about one-third are no longer under hormonal influence, and in these no benefit is obtained; that in the remaining two-thirds there is an improvement varying from complete control of the disease to an amelioration which varies in degree and in the length of time which the improvement lasts. The longest period of improvement in this series is 24 months. No other method of treatment has as yet achieved control of disseminated, widespread, and often terminal stages of breast cancer comparable to that following bilateral adrenalectomy.

Selection of Cases

In all the 56 adrenalectomized patients cancer of one or both breasts had been present for various periods of time and had been treated previously according to its stage and extent by appropriate methods. In every patient skeletal, visceral, or soft-tissue metastases were widespread and the expectation of life was very limited. The selection of patients was, in fact, simple: only those to whom nothing further could be offered were submitted to adrenalectomy. The operation was therefore put to a severe test and was deemed a justifiable experiment. It was soon found that patients with disseminated disease in the pulmonary lymphatics, with involvement of the pericardium and the heart, were not likely to benefit from adrenalectomy and that the

*Based on a Hunterian Lecture given at the Royal College of Surgeons of England on June 17, 1954.

operative risk in such cases was high. In fact, involvement of the lungs and heart to an extent which impaired vital function is regarded at present as the main contraindication for the operation.

Management

Pre-operative.—All the patients are carefully assessed, as regards the extent of the disease and the general state of health, by clinical, radiological, and chemical investigations. In addition the output of 17-ketosteroids and oestrogens is studied and the Thorn test for adreno-cortical function done. The pre-operative preparation consists in the correction of the blood state by transfusion and the administration of cortisone. In this series of patients cortisone only was used. There seemed to be no need for D.C.A. (deoxycortone) or for extra salt. Cortisone acetate is given in 100-mg. doses by intramuscular injection forty-eight, twenty-four, and one hour before the operation.

Post-operative.—During the operation and in the immediate post-operative period noradrenaline is used only if

there is a marked fall in the blood pressure. Noradrenaline is not used as a routine, only as an emergency measure. On the first post-operative day cortisone is given by injection in 100-mg. doses six hourly; this is reduced by a half on the second post-operative day; from the third to the fifth post-operative day 25 mg. of cortisone acetate is given by mouth six-hourly; this is further reduced to 75 mg. a day and finally to 50 mg. daily as a maintenance dose. Patients are given instructions about the need of extra cortisone during intercurrent illness or following an operation or an accident. Medullary failure occurs very rarely, sometimes several weeks or even months after adrenalectomy, and is corrected by noradrenaline.

The Operation

Bilateral adrenalectomy and oophorectomy can be done in one stage. The practice at present is to carry out bilateral oophorectomy and unilateral adrenalectomy in one stage and postpone the second adrenalectomy for seven days. The best approach to the adrenal is through the bed of the twelfth rib, the patient lying on her side, in the position usually adopted for renal operations. When the twelfth rib is small, it is necessary to remove the eleventh rib. The operation is technically simple, but the adrenal must be handled with care as it is friable, and in some patients there occurs a marked fall or rise in the blood pressure when the gland is manipulated. Haemorrhage is controlled by careful ligation of the adrenal veins, which show considerable anatomical variations, and with which the surgeon should be familiar. Accidents which can be guarded against are injury to the pleura, the renal vein, or inferior vena cava. In most patients convalescence is smooth, and the post-operative course gives rise to anxiety only in patients with cardiac or pulmonary involvement by disease or following operative difficulties.

Results

Mortality.—Of the 56 patients, 8 died following the operation, a mortality of 13.6%. The causes of death in these cases were: one from pulmonary embolus; one from cardiac arrest during the operation; two from renal failure on the sixth and twenty-first post-operative days; one from cerebral metastasis; and three from pleural and pericardial involvement by disease. A most careful study of these cases indicates that the very precarious state of the patient as well as the operative risk accounted for the deaths. It is interesting to note that there has been no operative death in the last 27 cases.

Failures.—Twelve patients derived no benefit at all from the operation: the disease progressed, and most patients died from it within a period of a few months. In 14 patients there was no alteration in the metastases, although some improvement in the general state of health and relief of symptoms was obtained. In four patients there was no relief of symptoms, although local improvement of the lesions was noted.

Successful Cases.—These patients have been studied as regards subjective and objective improvement. In 13 patients the results were remarkable, in the sense that bedridden patients with severe pain became ambulatory and no longer required pain-relieving remedies. The subjective improvement was accompanied by increase of weight and a return to a near-normal life. Objective improvement was assessed by healing of pathological fractures, alteration of osteolytic lesions to a normal bone structure, shrinkage of visible external tumours, such as the primary tumour, skin nodules, enlarged lymph nodes, and disappearance of metastases in the omentum, peritoneum, lungs, liver, and in the choroid. In one patient, nearly *in extremis* when adrenalectomized, with extensive destruction of the base of the skull, multiple cranial nerve palsies, and pleural, pulmonary, and intra-abdominal metastases, most lesions disappeared and the patient regained a near-normal state of health for a period of fourteen months, when the disease became active again

FIG. 1.—Case 1. Bilateral carcinoma of breast. Multiple skeletal metastases. Survival to date: 24 months after adrenalectomy. Marked increase in weight; regression of skeletal lesions. A, Moon-shaped face. B, Scars of bilateral adrenalectomy.

FIG. 2.—Case 2. Metastasis in humerus before and 10 months after adrenalectomy.

and the patient died fifteen months after adrenalectomy. So far, the longest survival period in this series is twenty-four months and the shortest six weeks. Examples reported here show regression of various types of lesions—skeletal, visceral, and soft tissue. Improvement can usually be noticed within a few days of the operation. If no improvement occurs within one week the case is likely to prove a failure.

Prognosis.—There is no method at present by which to forecast if adrenalectomy will be a success or a failure. Attempts have been made to correlate the results with the age of the patient, the extent of the disease, and the histological type of the primary growth. Both successes and failures were noted in all histological types, although Huggins and others think that the adenocarcinoma is more likely to regress than the carcinoma simplex or other varieties. The incidence of metastases in the adrenal is very high and reproduces accurately the histological variety of the primary growth. The Table shows the results in 48 patients.

Results in 48 Patients: Adrenalectomy for Breast Cancer

	Alive		Dead
	Subjective	Objective	
Excellent	13	10	1 (14 months)
Satisfactory .. .	22	16	1 (12 months)
No effect	7	14	9
Too early for assessment..	6	8	—
	48	48	11

Illustrative Cases

The following successful cases illustrate the benefit which has been achieved by adrenalectomy in some patients with advanced and disseminated breast cancer no longer treatable by other methods. The cases chosen show the effect on skeletal, pulmonary, and soft-tissue metastases.

Case 1. Aged 50. Right radical mastectomy in January, 1950, for a carcinoma simplex with involvement of axillary lymph nodes. Post-operative x-ray therapy. In August, 1951, left radical mastectomy for a histologically similar tumour; lymph nodes in axilla involved. Post-operative x-ray therapy. In January, 1952, multiple skeletal metastases in spine, ribs, and skull. Testosterone propionate given by injection. In July, 1952, bilateral oophorectomy; both ovaries infiltrated by metastases. In November, 1952, the skeletal metastases had spread widely. Nearly all the ribs and all the vertebrae were involved. The sternum was the seat of a large tumour; 17-ketosteroid excretion: 6 to 7 mg./24 hours. Bilateral adrenalectomy performed. This was followed by immediate relief of pain and a fall in the 17-ketosteroid excretion to 2.5 mg./24 hours, and the Thorn test showed no fall in the eosinophil count. Both subjective and objective improvement was very marked. The effect on the skeletal metastases in the skull, sternum, and spine was a return of the bones to a normal structure. The patient remains well to date, twenty-four months after adrenalectomy. Fig. 1 illustrates the patient's present appearance; there is an alteration in her face (moon-shaped) due to the cortisone; marked increase in weight and complete relief from pain.

Case 2.—Aged 42. Right radical mastectomy for a pleomorphic carcinoma of the breast in December, 1950. Post-operative x-ray therapy. In April, 1952, skeletal metastasis in lumbar and dorsal vertebrae. Pain relieved by x-ray therapy, but further metastases in the spine developed. From July to October, 1952, given testosterone propionate, but extensive skeletal

metastases found in right humerus (pathological fracture), skull, ribs, pelvis, femora; collapse of third lumbar vertebra. Patient was bedridden and in considerable pain on movement. 17-ketosteroids, 9.4 mg./24 hours. Bilateral adrenalectomy performed on April 9, 1953. Both adrenals contained metastases. Skeletal pain relieved within twenty-four hours. Rapid recovery; healing of pathological fracture of humerus and other skeletal metastases. Fig. 2 shows the right humerus before adrenalectomy and ten months later; Fig. 3 shows extensive osteolytic lesions of the skull before and five months after operation. The patient is ambulatory and remained well seventeen months after adrenalectomy.

FIG. 3.—Case 2. Osteolytic lesions in right parietal and frontal bones. Before and five months after adrenalectomy.

FIG. 4.—Case 3. Pulmonary metastases from carcinoma of breast before and three months after adrenalectomy.

Case 3.—Aged 53. In September, 1952, mastectomy and post-operative x-ray therapy for an adenocarcinoma of the right breast. In August, 1953, patient noticed "flashes of light" in the right eye with progressive visual impairment. Seen by Mr. E. F. King at Moorfields Hospital and found to have a large choroidal metastasis in the right eye. X-ray examination of chest showed extensive bilateral pulmonary metastases (Fig. 4). Bilateral oophorectomy and adrenalectomy in October, 1953; the right ovary contained a metastasis; no metastases in either adrenal. Rapid improvement followed; complete disappearance of choroidal metastasis within three weeks and nearly complete regression of pulmonary metastases within three months (Fig. 4). Patient remains well to date, twelve months after adrenalectomy.

Case 4.—Aged 35. In November, 1951, radical mastectomy for an adenocarcinoma of the right breast with metastases in the axillary lymph nodes. Post-operative x-ray therapy. In July, 1952, metastases in the ribs and dorsal spine with destruction of several mid-dorsal vertebrae and marked kyphosis. X-ray menopause and testosterone failed to control the disease. In November, 1953, there was widespread involvement of the skull, pelvis, lower dorsal and lumbar vertebrae, ribs, both scapulae, and both femora. Sternal puncture showed numerous malignant cells in the bone marrow. Bilateral adrenalectomy performed on November 10. Rapid recovery; complete relief of bone pain. Increase in weight by 2 stone (12.7 kg.) and return to duty as a nurse in an administrative capacity. Improvement lasted nine months. Died twelve months after adrenalectomy.

Case 5.—Aged 43. Left radical mastectomy for a carcinoma simplex of the left breast in March, 1950. Two years later, local recurrence in scar (Fig. 5,A) which was not controlled by radiotherapy. Bilateral oophorectomy and adrenalectomy in November, 1953. Rapid disappearance of lesion (Fig. 5,B). Remains well to date, twelve months after adrenalectomy.

Case 6.—Aged 39. Radical mastectomy for a carcinoma simplex of the right breast in January, 1951. Post-operative x-ray therapy. In May, 1952, carcinoma of the left breast which did not respond to x-ray therapy. In December, 1952, there was a condition of carcinoma-en-cuirasse on the left side of the chest wall; enlarged supraclavicular lymph nodes. No improvement from testosterone. In February, 1953, bilateral oophorectomy was done with temporary improvement. In October, 1953, there were extensive local disease; an orbital metastasis causing proptosis of the right eye; skeletal metastases in the pelvis and the right scapula; and a pleural effusion. Bilateral adrenalectomy was performed on November 24, 1953. This was followed by remarkable subjective and objective improvement: relief of pain, return to a normal life, and complete disappearance of the lesion on the right side of the chest wall and supraclavicular gland. Remains well to date, twelve months after adrenalectomy.

Case 7.—Aged 40. Right radical mastectomy for a late stage II scirrhous carcinoma of the right breast in October,

FIG. 6.—Case 7. Enlarged lymph nodes in contralateral (left) axilla following right radical mastectomy. This patient also had multiple skeletal metastases. A, Before adrenalectomy. B, Five months after adrenalectomy.

1949. Post-operative x-ray therapy. Three years and three months later, in January, 1954, metastases in pelvis, femora, and opposite axilla (Fig. 6,A). Bilateral oophorectomy and adrenalectomy in February, 1954. Both adrenals but not the ovaries involved by metastases. Uneventful recovery. Rapid disappearance of contralateral lymph node (Fig. 6,B): complete relief of pain from skeletal metastases to date, eight months after adrenalectomy.

Summary and Conclusions

A series of 56 patients is reported on whom bilateral adrenalectomy was performed for disseminated breast cancer. Extended survival on cortisone maintenance has been obtained, so far up to 24 months. In a proportion of cases both subjective and objective improvement has been achieved which has never been accomplished before by any other method of treatment. Relief of pain from skeletal metastases, regression of visible and palpable lesions, reossification of skeletal metastases, and union of pathological fractures have followed adrenalectomy. There is no method, so far, to forecast if a patient will be benefited by the operation or not. Beneficial effects have been achieved in about 60% of patients; and in a proportion of these—23% of all cases—the improvement was quite remarkable and surprising.

The risk of the operation is reasonable and maintenance of life on cortisone simple. Although there is no likelihood of any permanent effect, the results are encouraging, and it seems justifiable to advise the operation at an earlier stage of the disease.

I would like to express my thanks to the Medical Research Council for the provision of cortisone and to my colleagues at Westminster Hospital for their help and co-operation, especially to Dr. F. D. Hart and Dr. C. J. M. Clark for the medical care of the patients, to Mr. A. Jessiman and Mr. G. Westbury for the help at the operations and post-operative care, and to Miss Worcester, the sister in charge of my wards, and her staff, on whom fell the burden of nursing care of these very ill patients.

FIG. 5.—Case 5. Local recurrence following radical mastectomy and radiotherapy. A, Before adrenalectomy. B, Five months after adrenalectomy.

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PROBLEMS INVOLVED IN PREVENTION OF BACTERIAL COMPLICATIONS OF MEASLES

WITH SPECIAL REFERENCE TO PROPHYLACTIC SULPHADIAZINE*

BY

G. I. WATSON, M.D.
General Practitioner

There is general agreement that sulphonamides and penicillin have contributed greatly to the fall in the mortality of measles in recent years (*British Medical Journal*, 1952), but the need for further study of the prevention of morbidity arising as a result of measles is also recognized (*British Medical Journal*, 1953). Since this essay was submitted, the *Lancet* (1954), in discussing the prophylaxis of measles complications, makes the following statement: "In this country quite satisfactory prevention of bacterial complications can still be obtained by the simpler and cheaper method of sulphonamide prophylaxis. This is one of the few forms—if not the only form—of routine sulphonamide prophylaxis that can be generally recommended." Two questions, however, have not yet been satisfactorily answered. The first is whether sulphonamides are, in fact, effective in the prophylactic as opposed to the curative treatment of the bacterial complications of measles. The second is whether the preventive dose, if effective, is sufficiently lower than the curative to warrant the expense involved by putting every case of measles on a prophylactic, even when no evidence of bacterial infection is present at the onset of the virus illness.

Historical

Haerem (1943) attempted to evaluate the effect of sulphonamides as antiviral rather than antibacterial agents in patients, probably mainly adults, admitted to a military hospital with measles. The dosage was 1 g. four times daily for four days. He found no significant differences in the duration of fever or the stay in hospital between treated and control cases, and he could find no previous mention of the use of sulphonamides in measles.

Begg *et al.* (1947) attempted to assess the total bacterial and haemolytic streptococcal counts in measles cases nursed in an L.C.C. hospital, and made a subsidiary study of the value of sulphadiazine in such cases. They concluded that sulphadiazine in a dose of 0.25 to 1 g. daily according to age was "of very doubtful prophylactic value," but were dissatisfied with their controls. The ages of the children are not given.

Badr El-Din (1951) attempted to assess the possible value of chlortetracycline ("aureomycin") "as an anti-viral agent" in measles by attention to three things:

(a) the increase or decrease of "catarrhal signs"; (b) the development and fading of the rash; and (c) the presence or absence of complications. The ages of only some, possibly the youngest, of the children are given. They were treated in hospital. Two out of 10 controls developed bronchopneumonia. No case of acute otitis media was reported, and no complications occurred in cases treated prophylactically, either with chlortetracycline or with combined penicillin and sulphadiazine. He found that chlortetracycline, given in the phase before the rash, diminished the catarrhal signs and also the intensity of the rash, if given early enough. He interpreted these as actions of chlortetracycline on measles virus, but other possible interpretations are discussed below.

No report has been traced of the use of sulphonamides or antibiotics in measles treated at home, nor of any attempt to assess the prophylactic value of these drugs in relation to the age of the child, to its past medical history, or to the presence or absence of bacterial infection at the onset of its measles. The present paper is an attempt to do this, as well as to define more clearly the limits of the problem, and to suggest what still remains to be done in any future, more extensive investigations.

Present Investigation

From December, 1950, to May, 1951, I attended 142 cases of measles in a rural partnership practice in the south-east of England, and the notes made at the time of seeing these patients, many of whom were treated prophylactically, mainly with sulphadiazine, have provided the material for this paper. As my notes were not then made with this particular research in mind, desirable details have sometimes not been recorded. Details of late complications after the children were out of the house from their attack of measles have not been analysed, as I was not then the only doctor seeing them. Particular care, however, was being taken during the epidemic to determine what signs of bacterial infection were present in each child at the onset of measles, and what evidence arose later in the illness to show that bacterial invasion had occurred. The details in this respect are therefore as accurate as circumstances allowed, and were all observed and recorded by me.

In defining the virus illness for myself, I took as its onset the first day of fever or typical symptoms, such as coughing or sneezing; and the end as the day when the rash had faded from the abdomen. At this stage a child was allowed up in the house, and outside on the next suitable occasion; but it was not returned to school or other crowds until three weeks after the onset of the rash, so as to minimize the risk of bacterial infection for that time. The episode which appeared to throw open the air passages of the head and chest to bacterial infection was the rash, first in the form of Koplik's spots. As the rash faded, so the mouth and eyes visibly healed, and one pictured the whole epithelium of the head and chest gradually recovering its resistance. Each of these stages in the virus illness might be defined more exactly in terms of changes in the leucocyte count, as is suggested below.

Information about the drugs used is incomplete in respect of dosage. The system I used for prophylaxis as a rule was a dose of tablets daily that totalled one more than the child's age in years, up to a total of six, in divided doses—that is, a child of 2 would have three tablets (each 0.5 g.) daily, in halves, while a child of 5 or over would have six tablets daily, one at a time. The duration of prophylactic treatment was from the day the child was first seen until at least the day the rash began to fade from the legs, sometimes until the rash had completely faded from the abdomen. I usually gave out the tablets at the time of my visit, working on this basis.

*Based on the Sir Charles Hastings Clinical Prize Essay, 1954.