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Bilateral adrenalectomy as a palliative method of controlling metastic breast cancer

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BILATERAL ADRENALECTOMY AS A PALLIATIVE METHOD OF CONTROLLING METASTATIC BREAST CANCER

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INTRODUCTION

Breast cancer challenged medical men of antiquity as it does the present-day physician. The earliest medical record, written 3000 B.C. during the Egyptian Pyramid Age, contains a series of eight cases concerned with tumors of the breast. These ancients skillfully used caustics for tumor destruction. Surgical excision of localized mammary cancer was recommended in Galen's era. Le Dran (1), an enlightened French surgeon of the eighteenth century, first recognized lymphatic spread to regional nodes and reported the necessity of axillary node dissection. From Halsted's (2) concept of excising all suspected tissue in block has developed our present-day surgical technique of radical mastectomy.

The goal in the cure of breast cancer is the removal <u>en bloc</u> of the primary tumor with all of its areas of lymph drainage. This, of course, must be done before the disease has disseminated beyond the scope of surgery. It is after mammary cancer has disseminated by blood or lymph channels that the treatment is uncertain and the physician is in a quandary. His only recourse then is to attempt to control the metastases by manipulating the hormonal environment of the malignant cells. Bilateral Adrenalectomy has been done in an effort to upset

hormonal homeostasis so as to favorably modify the course of mammary malignancy. This thesis will present the operative method of Bilateral Adrenalectomy, and evaluate this procedure as a palliative method of controlling metastatic breast cancer.

EXPERIMENTAL DATA CONCERNING MAMMARY CANCER'S RELATIONSHIP TO GONADS AND ADRENALS IN ANIMALS

Early experimentation on mice showed that ovarian hormones influence the growth of mammary cancer, and are possibly a factor in its etiology. Loeb (3), in 1916, found that the removal of ovaries of female mice done before the age of six months led to a striking decrease in the incidence of breast cancer, but did not entirely prevent it. Cori (4) confirmed this in 1927. Lacassagne (5), in 1932, succeeded in producing mammary cancer in male mice by repeated injections of estrogen.

That the adrenal cortex could supplement the ovaries in the production of sex hormones was next to be experimentally proven. Price (6), in 1936, described within the adrenal cortex of young male rats, which were castrated early in life, a definite change that he called the X zone and to which he attributed the pubertal sex changes found in these rats. Fekete (7), in 1941, found in mice that, in spite of the absence of ovaries, considerable amounts

of estrogen were produced during later life; and he postulated the hormone's source was the adrenals which were hypertrophied and contained yellow nodules. Spiegel (8), in 1939, showed in guinea pigs, and Woolley (9), in 1939, in mice, that after orchidectomies in young males, tumors of the adrenal cortex developed with subsequent masculinization of the animal.

An attempt to counteract this carcinogenic effect of estrogen on the breast was the next avenue of investigation. Raynaud (10) and Murlin (11), investigating separately in 1939, showed androgens did have a detrimental effect on certain carcinomas in mice. Raynaud ovarectomized mice with mammary cancer metastases and remissions resulted. Shimkin (12), in 1945, found that adrenalectomy reduced the incidence of mammary tumors in mice as much as ovarectomy.

MAMMARY CANCER AND GONADAL HORMONES IN MAN

The relationship of the ovary to some cases of mammary cancer in women was first noted by Schinzinger (13) in 1889, at which time he suggested castration for advanced breast cancer. Beatson (14), in 1896, observed considerable clinical improvement in two cases of advanced mammary cancer in which he had removed the ovaries. Lett (15), in 1905, collected 99 patients who had

advanced mammary cancer and who previously had had their ovaries removed. He found 23 per cent showed much improvement and 13 per cent moderate improvement.

The removal of the ovaries to restrain breast cancer fell into disuse to be rediscovered recently and now again widely practiced. Adair (16), in 1942, reported that cancer of the male breast with metastases regressed after orchidectomy. Treves (17), in 1949, had 3 of 6 patients with metastatic cancer of the breast show a remission after castration. Relief of pain and healing of bone metastasis were noted.

Irradiation of the ovaries was first used by De Courmelles (18) in 1922 in treating breast cancer. Dresser (19) reported improvement in 43 per cent of 59 patients treated by irradiation of the ovaries; relief of pain and regression of metastases lasted up to three years.

The administration of testosterone to neutralize estrogens in inoperable breast cancer was used by Ulrich (20) in 1939. This form of therapy has been in common use for many years with benefit in some cases. Farrow (21), in 1942, treated 33 patients with skeletal metastases with testosterone propionate. One-half of the patients obtained relief from pain, but there was no clinical or X-ray evidence of control of the disease. He found that with massive doses of testosterone the

metastatic tumor's growth appeared to be stimulated.

However illogical the use of stilbesterol may appear, its use has produced striking regression in some cases. Haddow (22), in 1944, reported the results of treating 204 patients with stilbesterol for periods of one to nine months with some improvement in 26 per cent, although always relapse eventually took place. Nathanson (23) gave the following description of a series of women treated with large doses of stilbesterol:

> In a few cases a beneficial result was effected on the primary tumor. Ulcerations decreased in size or became epithelialized, masses became smaller. The favorable response occurred chiefly in older women and in younger women the course remained ulaltered or possibly accelerated.

RATIONALE OF ADRENALECTOMY FOR MAMMARY CANCER IN MAN

Huggins (24), in 1945, was the first to suggest bilateral adrenalectomy and also the first to practice it. His genius in physiological research, his accuracy of clinical observation, his surgical skill led him to try adrenalectomy in advance of the discovery of cortisone, only to abandon it until replacement therapy became available.

Adrenal tumors have long been known to cause virilism. Wilkins (25) collected from the literature

55 cases of adrenal tumors in children, 31 girls and 12 boys suffered from virilism; their urine showed an increased excretion of 17 ketosteroids. Twelve cases of feminizing tumors appeared in males.

The adrenal cortex as a source of sex hormones in man was to be experimentally verified. Frazer (26) found that a significant effect of adrenalectomy was the rapid fall in urinary 17 ketosteroids in the male and female. He determined that the total values of 14 mg. to 9 mg. as the average excretion of 17 ketosteroids; and he postulated that 5 mg. comes from the gonads, the remainder from the adrenal cortex.

Scott (27) has shown that after gonadectomy there is a preliminary fall in the beta 17 ketosteroids, and after a variable length of time, again the ketosteroids appear in the urine in considerable amounts. This he theorized was induced by the adrenal cortex. Dao (28) showed that following oophorectomy women continue to excrete significant and even large amounts of estrogenic compounds in the urine. He also found that in both males and females the removal of the gonads is followed by hypertrophy of the adrenal cortex. After adrenalectomy these estrogenic compounds are eliminated from the urine. In summation, evidence pointed to the fact that the adrenal cortex may normally be a source of sex hormones; and under

the stimulus of oophorectomy the adrenal cortex may hypertrophy to produce considerable amounts of these hormonal substances.

Huggins (29) realizing that the hormones formed in the gonads which sustain mammary cancer are formed also in the adrenal cortex, postulated that since certain cancers of the breast retain sufficient qualities of the cells from which they arise, the growth of the cancer may be stimulated or inhibited by the administration or withdrawal of appropriate endocrine substances. Thus adrenalectomy combined with ovariectomy surgically eliminates this hormonal stimulation of the malignant mammary cells. Of course, not all mammary cancers are hormone dependent, and even if hormone dependent at first, they may cease to be so.

INDICATIONS FOR BILATERAL ADRENALECTOMY IN BREAST CANCER

When dissemination of breast cancer occurs and the disease is no longer controllable by localized treatment, surgical or radiological, administration of androgens and estrogens may be tried. Endocrine control by the administration of hormones has many draw-backs and definite limitations, and so gonadectomy has replaced it in a number of cases.

Adrenalectomy removes the extra gonadal source of androgens or estrogens which might well be responsible for the failure of hormonal therapy or the reactivation of the neoplasm following castration. As Huggins (30) and Cade (31) have shown, the response of the cancer to adrenal ablation does not depend upon the loci of the metastasis, but upon the malignant cell's hormonal dependence. Skeletal, cutaneous, visceral, pulmonary metastases may equally benefit from adrenalectomy.

PRE-OPERATIVE MANAGEMENT AS SUMMARIZED FROM HUGGINS (29), CADE (31) AND PYRAH (32)

1. An accurate estimate of the extent and distribution of the neoplastic lesions is made. The site and extent of the primary tumor is noted. Enlarged lymph nodes in both axillae and supraclavicular fossae should be looked for. A careful radiological investigation of the thoracic cage, the entire vertebral column, the shoulder and pelvic girdles, humeri, femora, and the skull is advisable. Skeletal invasion is often surprisingly wide, and many lesions may be clinically silent. The presence of pulmonary, pleural, hepatic, and ovarian metastases is ascertained. Many patients present neurological lesions, one or more cranial nerve palsies, or incipient paraplegia. Intra-ocular and cerebral lesions should be specifically looked for.

2. An assessment of the general state of the patient is made, including the degree and distribution of pain and the nutritional state. Renal function is studied by an estimation of the blood non-protein nitrogen and by intravenous pyelograms. Hematological and bone marrow studies are made and any blood deficiency is made good before the operation. Chemical investigation includes, in addition to the sodium, potassium and chloride estimation, those of alkaline and acid phosphatase and the serum calcium.

3. Blood transfusion is important to correct a low hemoglobin and red cell count. Cortisone is given by intra-muscular injection in 100 mg. doses, forty-eight, twenty-four, and one hour before the operation. This is essential if bilateral adrenalectomy is done in one stage and before the second adrenal is removed in the two-stage operation: it is advisable even before the first adrenal is removed in a two-stage operation in case there is only one active adrenal. Before the operation an efficient intravenous cannula is inserted; this is connected to two bottles by a Y connection. One bottle contains blood; the other bottle, 5 per cent glucose containing 4 cc. of Nor-adrenaline. The administration of Nor-adrenaline should be discontinued as soon as the blood pressure is maintained.

OPERATION AS SUMMARIZED FROM HUGGINS (29), CADE (31) AND PYRAH (32)

Anesthesia

General anesthesia by the endotracheal route is most satisfactory. In view of the frequency of pleural involvement, the presence of pleural fluid, the limitation of respiratory movement by the operation position, and the chances of the pleura being opened during the operation, it seems safer to employ the greater control of respiratory function that this method gives. A light plane of anesthesia should be the rule. After induction with a small dose of pentothal, it may be maintained with nitrous oxide and oxygen supplemented with ether. Relaxation is achieved with one of the muscle relaxant drugs, very great care being taken that its action is entirely passed by the end of the operation.

Blood Pressure Changes

The blood pressure must be carefully checked throughout. Its level will tend to fall, sometimes severely, by induction of anesthesia, by alterations in position, and by blood loss. And it will tend to be raised by handling of the adrenal. The removal of the second gland, when both are removed together, frequently produces a severe fall; but in the two-stage operation

usually no such fall occurs, or only to a limited extent. Serious hypotension is usually best controlled by the Nor-adrenaline drip.

Anatomy of the Adrenals

Certain points in the anatomy of the adrenals are of surgical importance and worthy of mention. The glands are tethered in position by strands of fibrous tissue which form an incomplete capsule and traverse the areolar tissue around it. Huggins (29) likens these strands to "guy wires" in that they form the attachment to the kidney below and more firmly to the diaphragm above. The arterial supply from the aorta, inferior phrenic, and renal arteries is seldom visualized as separate arteries, as these break up before reaching the adrenal into numerous small vessels which entirely surround the adrenal. These numerous arterioles form a fine vascular network and are intimately connected with fibrous strands.

The venous return differs somewhat on both sides. On the right side a very short vein leaves the hilum of the gland anteriorly to enter the inferior vena cava. Common variations occur, such as duplication of the vein, both entering the cava separately and emerging from one or other pole of the gland. On the left side, the adrenal vein is larger; it terminates occasionally directly

in the left renal vein, but much more frequently it enters the inferior phrenic vein as a tributary, or joins with it to form a short trunk which enters the renal vein. The veins are anterior to the adrenals and cannot be seen till the gland has been sufficiently freed to be displaced laterally and rotated.

On the left side, the splenic artery is an important anterior relation and is frequently seen at the upper part of the adrenal pursuing a tortuous course. The relation between the adrenal and the kidney differs on each side; the right is, in fact, as its name implies, "a suprarenalcapsule," it sits like a cap on the upper pole of the right kidney, and the left adrenal is found mostly on the medial aspect of the upper third of the left kidney. Anterior to the gland and separated from it by some loose but vascular areolar tissue lie the main venous channels, vena cava on the right, and the much more slender inferior phrenic vein on the left.

Approach

The best exposure is obtained by a postero-lateral approach, the patient lying in the lateral position, usually employed for renal operations. The head and foot of the operating table are lowered. The incision is made over the twelfth rib and after division of the muscles

this rib is excised to increase exposure. The pleural reflection is seen passing horizontally across the bed of the twelfth rib, and if opened, the hole is sutured immediately. The subcostal vessels and nerves are exposed and the fascia incised exposing the peri-renal fat.

Removal of the Adrenal

The kidney is displaced downwards and laterally, and the adrenal is identified as a flat, yellow structure with its surface mammilated. The gland is very friable and yet it is desirable to remove each gland intact and in one piece. Any piece-meal technic is apt to leave behind fragments which are capable of great regeneration. The gland must be handled with the utmost gentleness. Too much manipulation with the fingers inevitably tears the gland. Sharp dissection with scissors combined with a little blunt dissection is the best way to remove the gland. The only blood vessel that commonly needs ligation in the adrenal region is the adrenal vein, which is situated on the anteromedial aspect at the junction of the middle and lower thirds of the gland. It can be identified since it is larger than the other vessels, being about 4 mm. in diameter.

If a one-stage operation is the surgeon's choice, the patient is turned on the opposite side, redraped with

sterile linen and the other adrenal is removed as in the above procedure.

If the ovaries have not been removed previously, oophorectomy and unilateral adrenalectomy is usually done in one session, the second adrenal being removed seven to ten days later.

According to Cade (31), the difficulties encountered during adrenalectomy are (a) unexpected change in blood pressure, which is controlled by suitable intravenous medication; (b) opening the pleura is to be meticulously avoided, and if encountered the hole is to be closed immediately; and (c) hemorrhage.

POST-OPERATIVE MANAGEMENT

Cade (31) reported that following the operation cortisone acetate is given in 100 mg. doses every six hours intramuscularly for one day; it is reduced to two doses of 100 mg. each on the first post-operative day, and continued orally in 25 mg. doses six-hourly for two days. Cortisone is further reduced to 75 mg. on the fourth post-operative day, and finally from the sixth post-operative day most patients are maintained on a total of 50 mg. per day orally. In this series of 55 patients cortisone only was given as replacement therapy; there was no need for desoxycorticosterone, and this has

not been used. With a normal salt intake, all patients on cortisone maintenance remained in sodium and chloride balance.

Intravenous hydrocortisone is reserved for emergencies arising from post-operative complications, such as infections, pulmonary embolism, bronchopneumonia, or thrombosis. The amount required depends on the seriousness of the condition and at times may be very high. Hypotensive crises may occur quite suddenly, not only in the immediate post-operative period, but sometimes several weeks or even months after adrenalectomy. Increased cortisone and temporary administration of Nor-adrenaline and a small blood transfusion are usually effective and a normal blood pressure is achieved.

Huggins (30) administered cortisone acetate 50 mg. intramuscularly every four hours on the first post-operative day. Five milligrams of desoxycorticosterone acetate intramuscularly and three grams of sodium chloride orally were also given. The second day post-operative cortisone acetate was reduced to 50 mg. intramuscularly every twelve hours. Therapy also consisted of 3 mg. of desoxycorticosterone acetate and 3 gm. of sodium chloride. The dosage of steroids is gradually reduced until the sustaining dose of cortisone acetate (25 mg. to 50 mg. daily) is reached about one week after the operation; maintenance

therapy does not require desoxycorticosterone acetate. After one week the maintenance dose of cortisone is given by mouth. The diet is supplemented with 2 to 4 gm. of sodium chloride daily. Blood lost at operation is replaced and systolic pressure is maintained above 100 mm. mercury by slow intravenous injection of a vasopressor if needed. The total amount of fluid injected during the first day should probably not exceed 1500 cc. Acetylsalicylic acid (.6 gm. orally) is given when the temperature is 38° C. or higher. Patients are ambulated in 24 to 48 hours after adrenalectomy.

BODY METABOLISM ON CORTISONE MAINTENANCE

Cade (31) adjusted cortisone dosage on the basis of a sense of well-being, weight maintenance, and the strength of the appetite. No laboratory test helps define the eucorticoid state. The average maintenance dose of cortisone is 50 mg. per day; it varies, however, from 37 mg. to 75 mg. in individual patients. Increased cortisone needs are also experienced in time of stress or during an intercurrent illness.

To insure that patients understand the importance of accurate cortisone replacement, instructions are given verbally to the patient and also to a relative. In addition, printed instructions are given to the patient

before leaving the hospital.

According to Pearson (33), if cortisone is discontinued, within 24 hours the patient experiences malaise, lethargy, anorexia, and weakness. In the next 24 hours, the patient is giddy in the upright position and feels too weak to leave the bed. After 72 hours he has symptoms of nausea and vomiting, diarrhea, stupor. Objectively his blood pressure is low, although not to shock levels if the patient remains horizontal; his skin is cold and dry, and his pulse is weak and rapid. On the administration of cortisone, within 12 hours the patient was ready to eat and to ambulate, and he felt well.

Pearson's electrolyte studies during cortisone withdrawal showed the following. There was a prompt fall in serum sodium without a loss of sodium chloride in the urine. Daily urine volume fell sharply and there was a prompt gain in body weight. When cortisone was readministered there was a fall in body weight and an increase in urine volume, serum sodium returned to normal. Serum potassium remained normal. Hypoglycemia failed to develop. Pearson thus postulated that intravenous cortisone is the crux of therapy for adrenal insufficiency. The indiscriminate use of saline and water solutions must be carefully weighed against the possibilities of an already expanded extracellular fluid or water

intoxication. In hypotension, vasoconstrictors are best unless there is specific indication to warrant bolstering the blood volume. The administration of 100 mg. of cortisone or hydrocortisone in 500 cc. of 5 per cent glucose in water by continuous intravenous drip over a four-hour period will usually bring the patient out of an adrenal crisis in 4 to 6 hours.

A DESCRIPTION OF PATIENTS WITH REGRESSION OF ADVANCED BREAST CANCER FOLLOWING ADRENALECTOMY

Huggins (34) said that cases in remission appeared in good health and were somewhat obese, having gained 10 to 20 kg. These women showed much to complete subsidence of pain, stabilization, or healing of osseous lesions, disappearance of pleural effusion, and regression and healing of recurrent lesions in post-mastectomy scars. All have hot flashes of the post-menopausal kind, which is regarded as a favorable prognostic sign.

Pyrah (32) explained that where the operation was followed by a major remission of the malignancy, there was concomitant subjective improvement, with a feeling of well-being in the immediate post-operative period; and the appetite was rapidly regained. In most such cases, pain, which may have been previously severe, disappeared within 48 hours of operation. Where the operation was not

followed by much regression of growth there was usually a feeling of well-being, and pain was often relieved.

Cade (31) reported that in the good remissions obtained there was early and rapid relief of pain. Patients confined to bed, unable to feed themselves, or to move because of skeletal pain, became ambulatory and returned to a near normal life. There was disappearance of cutaneous masses, intra-abdominal masses, intra-ocular metastasis. Recovery from blindness, from cranial nerve palsies, and return of power in the limbs following early paraplegia from spinal compression was observed. Osteolytic skeletal metastases recalcify and pathological fractures heal. Subjective and objective improvements are not always concomitant. In some patients who subjectively are well, there is no demonstrable improvement in the lesions. The length of time the improvement lasts varied from a maximum of 20 months achieved so far to 4 months.

ANALYSIS OF A SERIES OF CASES OF BILATERAL ADRENALECTOMY FOR METASTATIC BREAST CANCER

Huggins (34)

18 women, ages 29 to 59, with bilateral adrenalectomy and oophorectomy.

8 died 47 days to 16 months after operation.

10 had a good remission despite previous failure of ovarian irradiation and testosterone.

19 women, ages 44 to 70, all under 52 years of age had X-ray sterilization; all had bilateral adrenalectomy.

9 died from 1 month to 7 months after operation.

10 are still in remission.

14 cases that were observed 2 years:

6 died.

1 living unimproved.

7 in remission.

Pearson (33)

12 women with bilateral adrenalectomy and oophorectomy.

7 died in from 18 to 228 days.

9 had subjective improvement from 14 to 264 days.

5 had objective improvement from 82 to 264 days, being able to perform their normal activities in a nearly completely unrestricted manner.

Dao (28)

50 women with bilateral adrenalectomy and oophorectomy.

20 responded favorably showing regression of neoplastic involvement in one or more of the following areas: local recurrent lesions, osseous metastases, pleural and pulmonary involvement.

Taylor (35)

17 women had bilateral adrenalectomy and oophorectomy.

7 had a regression of the metastatic activity of the cancer for 75 to 365 days.

9 had subjective improvement but no demonstrable regression of the cancer.

1 had no improvement.

Pyrah (32)

19 women that had bilateral adrenalectomy and oophorectomy.

7 died; one was a post-operative death.

2 are alive with no improvement.

10 had a remission.

Lawrence (36)

14 women that had bilateral adrenalectomy and oophorectomy.

5 women had objective improvement.

4 had no improvement.

1 died too early for evaluation.

2 just recently operated had moderate improvement.

Cade (31)

46 women had bilateral adrenalectomies, all previously having had ovaries eliminated by surgery or irradiation.

8 died as a result of the operation.

9 patients were very much improved.

12 patients had a moderate improvement with existing lesions fading away, but some new ones appearing.

11 women had no improvement and died within one to five months.

6 were too early for assessment.

Randall (37)

20 women following bilateral adrenalectomy and oophorectomy:

2 died within 30 days.

9 women had subjective improvement.

7 women had a remission of from four months to one year.

SUMMARY OF THE RESULTS OF BILATERAL ADRENALECTOMY FOR ADVANCED BREAST CANCER IN 214 CASES

Author	Objective and Subjective Remissions	Subjective Remissions	No Remissions
Huggins (34)	20 or 54%	--	17
Pearson (33)	5 or 31%	9	7
Dao (28)	20 or 40%	--	30
Taylor (35)	7 or 41%	9	1
Pyrah (32)	10 or 53%	--	9
Lawrence (36)	7 or 58%	--	5
Cade (31)	21 or 53%	--	19
Randall (37)	7 or 39%	9	2
TOTALS	97	27	90
Percentage of 214 cases	45%	13%	42%

Operative Mortality

Huggins (29) reported, in 1952, that bilateral simultaneous adrenalectomy had been performed on 42 patients with two post-operative deaths. There had been no operative mortality in the last 38 consecutive cases.

Cade (31), in 1954, had done 46 bilateral adrenalectomies for advanced breast cancer with 8 post-operative deaths. Three deaths were the result of the disease widely involving the lungs, the pericardium, and the heart, thus interfering with vital function. Two deaths were due to renal failure, one from tumor emboli in the kidneys, the other from thrombosis of the left renal vein. In this case, there was difficulty in controlling hemorrhage from the left adrenal vein, the variation of the venous system of the adrenals not then being clearly appreciated. Pulmonary emboli, cardiac arrest, and cerebral metastasis accounted for the other deaths. In Cade's hands the two-stage operation was much safer than removing both adrenals in one stage. He had 2 deaths in 39 two-stage operations, and 4 deaths in 11 one-stage operations.

Pyrah (32) reported, in 1954, one post-operative death in 22 bilateral adrenalectomies and bilateral oophorectomies.

Randall (38), in 1954, following bilateral

adrenalectomy and bilateral oophorectomy in 20 patients, had two post-operative deaths. One was a 73-year-old woman with massive intra-abdominal metastases and ascites, who died of cardiac failure two hours after cardiac arrest and resuscitation during surgery. The other died 18 days after operation of bronchopneumonia complicating extensive metastatic breast cancer.

ACCESSORY ADRENAL GLANDS

Accessory cortical nodules were said by Graham (38) to have been first described by Morgan in 1740. Since that time portions of adrenal cortical tissue have been found related to the liver, pancreas, mesentery, and the genital tract. Jaffee (39) noted that some of the larger accessory cortical nodules contained both cortex and medulla.

Graham (38) studied 100 patients for aberrant adrenal tissue in the celiac plexus region. Sixty-eight had no accessory adrenal tissue. Thirty-two had accessory adrenal tissue with 16 containing both cortical and medullary tissue, and 16 consisting only of cortical tissue. These accessory glands averaged 7 x 4 x 3 mm. They were found 2 cm. to 3 cm. from the midline and between the origin of the celiac and the superior mesenteric arteries. Fifty per cent were left of the midline,

19 per cent to the right of the midline, and only two glands were midline.

The origin of these aberrant glands is attributed to an embryological developmental defect. Graham postulated that this aberrant adrenal tissue would be capable of supporting life following removal of both adrenal glands.

ADRENAL METASTASES OF BREAST CANCER

Cade (31) found that in a series of 40 patients with breast cancer, 22 had adrenal metastases. The adrenal medulla showed a greater predilection for metastatic deposits than the adrenal cortex. This was also noted by Huggins (34). From the examination of the removed adrenals, Cade observed that nearly all the metastases originated in the medulla, remain for a time localized to it, grow locally for a time, and eventually invade the cortex. Less frequently, minute deposits are found scattered throughout the cortex and the medulla. Cade speculated that the bilateral replacement of the entire adrenal substance by metastases could account for the so-called "spontaneous" regression occasionally recorded.

DETERMINATION OF PROGNOSIS BY THE HISTOLOGICAL APPEARANCE OF THE MALIGNANT BREAST CELLS

Huggins (34) reported that the microscopic

appearance of the original neoplasm was of value in determining prognosis. He divided breast carcinoma into four groups: (a) Adeno-carcinoma with a preponderance of gland formation, 15 cases; (b) Papillary carcinoma, 4 cases; (c) Duct cell carcinoma, 8 cases; (d) Undifferentiated carcinoma, 16 cases. Response to bilateral adrenalectomy was present in none of the undifferentiated carcinomas, one of the duct cell carcinomas, sixteen of the papillary and adeno-carcinomas. It was his opinion that formation of acini in adeno-carcinoma is a positive process directly attributable to secretion induced by hormones. Elimination of the supporting hormones from the internal environment of the adeno-carcinoma changed the cell metabolism sufficiently to stop secretion causing the acini to collapse and the cells to shrink with subsequent benefit to the patient.

Pyrah (32) corroborated that tumors of the alveolar or adenomatous structure had responded most favorably to adrenalectomy, although it seemed unwise to rely on only one biopsy before rejecting a case, as two of the cases with the biopsy specimen taken from different areas of the tumor were reported as showing duct cell carcinoma in one area and alveolar cell carcinoma in another area. And one of the cases reported as a spheroidal cell carcinoma responded favorably to adrenal ablation.

Cade (31) studied 21 patients following adrenalectomy and reported that the histological type of tumor can not be considered reliable in assessing the likely result of adrenalectomy. His conclusion was based upon controlling the malignancy in three patients whose cancer was histologically undifferentiated carcinoma of the breast.

CORTISONE CONVERSION PRODUCTS PREJUDICING THE EFFICACY OF ADRENALECTOMY

The possibility of body metabolism converting cortisone acetate into a hormone that will support breast cancer is being experimentally scrutinized. Burstein (40) reported that Compound E (17 hydroxy-11-dehydrocorticosterone) can be converted to Compound F (17 hydroxy-corticosterone) in liver perfusions and patients with Addison's disease. The conversion of Compound F to Compound E was demonstrated in intact human, but not in perfused liver.

Zimmermann's (41) studies on adrenalectomized patients showed that the administration of hydrocortisone acetate caused an increase in both Compound E and F. Also the administration of cortisone acetate orally or intramuscularly caused a prompt increase in the output of Compound E and F and another substance he referred to as N.

Thus it seems that Compounds E and F are metabolically interchangeable, although the tissue involved in an adrenalectomized human is unknown. And the replacement

hormones are converted to various other substances in the body before being excreted. The specific hormones resulting from the body metabolizing cortisone or desoxycorticosterone are unknown, but the possibility exists that a hormone which will support breast cancer may result from this metabolism.

SUMMARY

Certain malignancies of the breast are dependent on hormonal activity and can be controlled by the withdrawal of these hormones. The adrenal glands are extra gonadal sources of these specific hormones and bilateral adrenalectomy with oophorectomy removes this source of stimulation to the breast cancer. The operation is compatible with prolonged survival on replacement therapy with cortisone. The most striking effects of adrenalectomy are relief of pain, improvement of nutrition, increased weight and objectively the regression and disappearance of disseminated cancer in the skeleton, the viscera and the soft tissue.

This review of the medical literature showed that bilateral adrenalectomy in 214 cases of advanced breast cancer resulted in 97 patients, or 45 per cent, having an objective and subjective remission. Huggins (34) observed 7 patients still in remission after two years.

The other authors had not observed their patients for a two-year duration post-adrenalectomy. Thirteen per cent of the patients had a subjective improvement only, and 42 per cent showed no remission.

The operative mortality of bilateral adrenalectomy for metastatic breast malignancy varied with the operator and his selection of patients. And since the surgery was done under the adverse conditions of advanced malignancy, the operative mortality is difficult to evaluate. Huggins (29), doing 42 bilateral adrenalectomies in one stage, had a 4.8 per cent mortality, and no deaths in the last 38 cases. From Cade's (31) work it would seem that the two-stage operation has a lower mortality than if both the adrenals are removed in one stage.

Determination of prognosis by the histological appearance of the malignant breast cells is uncertain. Pyrah (32) found that multiple biopsies from the same tumor would in some cases give a different histological type of cell. Cade (31) had remissions in three patients with undifferentiated carcinoma of the breast. It could be postulated that, while adeno-carcinoma of the breast has a better prognosis for remission from adrenal ablation, a biopsy of undifferentiated carcinoma does not mean a hopeless prognosis.

The question arises as to why does a patient in

a post-adrenalectomy remission sooner or later have a re-extension of the cancer. The explanation could be that accessory adrenal tissue hypertrophies and becomes capable of supporting the hormonal dependent malignancy; or some body tissue acquires the function of metabolizing cortisone to a gonadal-like hormone; or finally the cancer's metabolism changes so that a cell previously dependent upon hormonal stimulation for survival becomes autonomous.

CONCLUSION

Adrenal ablation seems to be a fundamental advance in the conception that both the cause and remedy of certain cancers lies within the body's physiological processes which affect the maintenance of cell nutrition and the function of cell division and hence life itself.

Bilateral adrenalectomy with gonadectomy does give encouragement in the pursuit of advanced mammary cancer control; and, in my opinion, is a valuable palliative method of controlling metastatic breast carcinoma.

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