

CARCINOMA OF THE BREAST: THE STATUS OF PRESENT THERAPY WITH SPECIAL REFERENCE TO A CASE TREATED BY BILATERAL ADRENALECTOMY AND OOPHORECTOMY

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The treatment of carcinoma of the breast has undergone changes throughout the history of surgery. The Halsted operation has held the field for many years; but even Halsted,¹ in 1898, included clearance of the supraclavicular fossa as part of his radical mastectomy in most cases. Although his followers largely abandoned these refinements, there has been a renewal of these operative extensions, e.g., Andreassen and Dahl-Iversen² clear the supraclavicular region; Margottini,³ Urban⁴ and Adair⁵ excise the internal mammary group of glands by a block dissection in selected cases. Saunders and Griffin⁶ have even suggested that in certain cases a bilateral mastectomy is necessary because their figures indicate that bilateral involvement occurs in 7-10% of patients with breast carcinoma.

On the other hand McWhirter⁷ claims better results, in the later cases particularly, with a less extensive (so-called conservative) mastectomy, followed by deep X-ray therapy. His results have supported such procedures, but it has been maintained that indecision

resulting from these arguments has led to less well performed operations.

Peters⁸ states: 'The McWhirter technique has produced impressive 5-year survival rates. However, from the data presented, whether it be a comparison on the basis of statistical 5-year survival, theoretical principles, or basic fundamentals, the evidence supports radical mastectomy in preference to simple mastectomy together with post-operative radio-therapy in the treatment of operable breast cancer.' He argued that in early carcinoma of the breast there may be axillary metastases, not observable clinically, which cannot be removed by simple mastectomy; reliance must then be on deep X-ray therapy to destroy these cells.

The main doubt is whether deep X-ray therapy can really destroy all carcinoma cells. Reliable clinics employing routine pre-operative radiation followed by radical mastectomy within a period of one year, show microscopic evidence of viable carcinoma cells, not only in the involved axillary nodes, but also in a high

percentage of the primary lesions. This has been proved despite various radiation techniques and the employment of extremely heavy radiation. 'Acceptance of a method leaving cancer cells behind is most unattractive, especially when a method is available affording a reasonable opportunity to eradicate these cells, the growth of which is unpredictable and certainly inevitable'.⁸

'Radical mastectomy is a valuable therapeutic weapon that today is to some degree in disrepute as it has been used indiscriminately, often in patients whose disease is entirely beyond the reach of the surgeon. The disappointing results obtained by the operation done in these circumstances have led surgeons to perform it carelessly. Bad selection is added to bad surgical technique with disastrous consequences to the patient.' This statement by McDonald, Haagensen and Stout¹¹ is true because it is well known that an operation which cuts through carcinoma cells is a useless surgical measure and actually reduces life by about 10 months.¹²

The argument in favour of the less extensive or the more radical procedure is dissolved if one definitely classifies cases of carcinoma of the breast as operable or not. The stages described by various authors (Table I) have not been uniform.

These methods of staging do not include features such as size of tumour, duration, rate of growth, site, age and histology.

Geschikter³³ points out that a tumour 1-1.5 cm. in diameter, of average duration of 3 months, has metastases in the axillary glands in 25% of cases; and a tumour 5 cm. or more in diameter, which has been present for a year or more, has metastases in the axillary

Stage	Description	% Survival	
		5-year	10-year
III.	Skin dimpling or nipple retraction. Mass over 6 cm. in diameter attached to fascia; a few axillary glands ..	38%	21%
IV.	Skin oedema or ulceration or skin nodules or acute inflammation. Diffuse tumour infiltration or rigid fixation to chest	16%	8%
V.	As above and nodules away from the periphery of the breast. Extensive axillary or supraclavicular nodes and distant metastases	3%	0%

It is unfortunate that most surgeons do not favour formulae in medicine. The 'clinical index of malignancy' in breast carcinoma as formulated by Lee and Stubbord,³⁵ and used in conjunction with staging, is of considerable value.

The Clinical Index of Malignancy (C.I.M.) is derived from the formula $1L+2A+3S+4R+5E$, as modified by Richards.³⁴ Points are assigned as follows:

Lactation (L)	..	Absent—0. Present—9.
Age (A)	Before menopause—1. 4 years or more after menopause—2. Commencement with or up to 4 years after menopause—4.
Site (S)	Outer quadrant, no lymph nodes—1. Inner quadrant, no lymph nodes—2. Outer quadrant, with nodes—3. Inner quadrant, with nodes—5.
Rate of Growth (R)		Slow—1. Moderate—2. Fast—3. Rapid (inflammatory)—4.

TABLE I

	Stage I	Stage II	Stage III	Stage IV
Steinthal ⁹ ..	Mass in breast	+ Axillary glands	.. + Local metastases ..	+ Distant metastases.
McWhirter ⁷ ..	Mass ± ulceration	+ Axillary glands	.. + Fixation to pectoral fascia	Late inoperable cases
Cade ¹⁰	Mobile mass ± attached to skin	+ Axillary glands	.. + Skin nodules	+ Generalized spread

glands in nearly all and involvement of internal viscera in 90% of cases. He estimates that a carcinoma of the breast increases in diameter by 1 cm. in 3 months on the average and correlates the size and duration with the 5-year survival rate (Table II).

TABLE II

Size	5-year Survival Rate
Less than 1 cm. in 6 months	84%
1 cm. in 6 months	63.5%
Over 1 cm. in 3 months	18%
Inflammatory (rapid growth)	4%

Richards³⁴ suggests the following staging (Table III):

TABLE III

Stage	Description	% Survival	
		5-year	10 year
I.	Breast mass 1-3 cm. in diameter ..	81%	59%
II.	Breast mass 3-6 cm. and a few small axillary glands	54%	28%

Stage or Extent (E)	I—1. II—2. III—3. IV—4. V—5.
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A total (by the formula) of 10-30 points indicates that the malignancy is low; 31-40 points indicate intermediate malignancy; and over 40 points indicate a highly malignant and extremely unfavourable condition.

The identification of cases as categorically inoperable seems an essential part of the approach to this problem. Haagensen and Stout¹² a decade ago gave criteria of inoperability based upon careful assessment of the clinical picture. These criteria (almost the same today) may be summarized as follows:

1. When extensive oedema involves more than one-third of the skin over the breast.
2. When satellite nodules are present in the skin over the breast.
3. When the carcinoma is of the inflammatory type.
4. When any 2 or more of the following signs of locally advanced carcinoma are present:
 - (a) Ulceration of the skin;
 - (b) Oedema of the skin of limited extent (less than one-third of the skin over the breast);

- (c) Fixation of the tumour to the chest wall;
 - (d) Axillary lymph nodes measuring 2.5 cm. or more in transverse diameter;
 - (e) Fixation of axillary lymph nodes to the skin or the deep structures of the axilla.
5. When there is oedema of the arm.
 6. When, in patients with clinically involved axillary lymph nodes, a supraclavicular dissection reveals metastasis in the supraclavicular lymph nodes.
 7. When, in patients with clinically involved axillary lymph nodes, a biopsy of the internal mammary lymph nodes reveals metastases.
 8. When X-ray study of the skeleton reveals metastases.
 9. When X-ray study of the lungs reveals metastases.
 10. When palpation of the liver suggests that it contains metastases.

SUPRACLAVICULAR AND INTERNAL MAMMARY LYMPH NODE METASTASES

The problems of extension to the supraclavicular and the internal mammary groups of lymph nodes are very much to the fore at present.

The Supraclavicular Lymph Nodes

In the Presbyterian Hospital, New York, 21.8% of the patients treated by radical mastectomy between the years 1915 and 1934, and who were found to have axillary metastases, later developed clinical evidence of supraclavicular metastases.¹¹

Andreassen and Dahl-Iverson² performed 98 dissections and reported that 33.4% of patients who had metastases to the axillary lymph nodes also had occult supraclavicular involvement of lymph nodes.

The subclavicular (apical) lymph node is supplied not only by the well-filtered system from the axilla and from the breast, but also by direct unfiltered lymphatic channels—including the more lateral pathway through Rotter's node (the interpectoral gland).¹¹ Moreover, the distance between the subclavicular node mentioned and the supraclavicular or 'sentinel' node, situated at the junction of the subclavian and internal jugular veins, is only 2 cm. Extension to the supraclavicular gland makes the case categorically beyond the scope of surgery but 'experience has taught us that, when metastases have reached the subclavicular group of lymph nodes, operation never achieves cure'.¹¹ In other words, involvement of the apical group of lymph nodes places the patient in this serious category of absolute inoperability.

The Internal Mammary Group

Hanly and Thackray¹³ have studied this group of glands. They occur mainly in the first 3 intercostal spaces with another group on each side in the 6th intercostal space. Dahl Iversen and Soerensen¹⁴ in 53 patients who belonged to the operable group (using Haagensen and Stout's classification) found 19% had involvement of the internal mammary gland; when there were metastases of the axillary lymph glands the figure was 47%. Margottini³ found 5% involvement of the internal mammary glands in stage I carcinoma. When there were axillary glandular metastases, the figure was 27.7%, and when the carcinoma was in the inner quadrant of the breast, as high as 40.5%.

The extensive attack on carcinoma of the breast by more radical procedures has been advocated by Urban⁴ and Urban and Baker.¹⁵ Adair⁵ states: 'There is no

effective substitute for meticulous radical surgery and extension of surgery should include: (1) removal of the nodes in the neck, (2) removal of the clavicle, (3) removal of the nodes along the internal mammary artery, (4) removal of involved ribs, (5) routine removal of the axillary vein, and (6) interscapulothoracic amputation when necessary.' He is strongly against treatment by radiotherapy after simple mastectomy.

Haagensen and Stout¹² perform a routine biopsy of the 2nd intercostal space (for investigation of the internal mammary group of glands) and also a simultaneous biopsy of the supraclavicular region. This has given them a more precise indication for radical surgery. It is of interest that they then perform a radical mastectomy for the operable cases; the others receive only radiotherapy. They summarize: 'It may be justifiable in the light of what we already know, to carry out block dissections of the internal mammary chain in certain types of cases, but this should be done only when the supraclavicular region, as well as the internal mammary region in the 1st intercostal space, has been proved by biopsy to be free of carcinoma. Cases fulfilling these conditions are few. We must not uselessly penalize a large proportion of our patients with this trying disease by subjecting them to indiscriminate internal mammary block dissection that can hope to benefit only a few.'

It is apparent that in a stage-I carcinoma in which there is a mobile mass there is a 5% chance of involvement of the internal mammary chain, and when there are extensions in the axillary lymphatic gland there is a chance of extensions to the internal mammary and supraclavicular lymph glands in one-third to one-half of the cases.

Suggested Staging

It seems more reasonable today to classify cases as follows:

Stage 1: Clinically undiagnosable carcinoma of the breast in which there is a mobile unattached mass, without any extensions, and in which there is no attachment to the skin or suspicion of an inflammatory nature. In this stage a biopsy by wide excision, and naked-eye as well as microscopic examination, confirms the diagnosis. Permission should have been granted before operation to perform a radical mastectomy, which is then proceeded with. If the microscopic appearance shows a very actively growing tumour, there is some justification for removal of the ovaries (either then or later), for it is in this type of patient that it is most likely that the 5% chance of extension to the internal mammary glands has already occurred. Particularly is this so if this type of growth is found in the medial half of the breast.

Stage 2: Early diagnosable carcinoma of the breast. The features present are early tacking to the skin or increased elevation of the affected breast on contraction of the pectoral muscles, with a mass palpable with the flat of the hand. In these cases a biopsy is often done, but is usually not needed. Radical mastectomy is necessary. When the microscopy shows a very actively growing tumour, a bilateral oophorectomy may be performed as well in the pre-menopausal woman. In all stage-1 and stage-2 cases a careful examination of the

axillary tissue must include serial histological sections to determine the presence of involved lymph nodes microscopically, although these may not be evident clinically. If the involved nodes are found, the treatment should be that for stage 3.

Stage 3: Carcinoma of the breast, still operable according to the Haagensen and Stout classification, but excluding the additional procedures of supraclavicular and 2nd-intercostal-space biopsy. When the categorically inoperable features are excluded, there remains the condition of a mass in the breast with ulceration of the skin, limited oedema of the breast, fixation of the tumour to the chest wall, lymph nodes in the axilla measuring 2.5 cm. or less, and fixation of the axillary nodes to the skin or deep structures. These features may occur as single items additional to the mass in the breast. They never occur together in this stage. In nearly half the cases there is the likelihood of extensions to the internal mammary and supraclavicular glands. It is therefore necessary in this group to advise routine oophorectomy as well in pre-menopausal women.

Stage 4: Categorically inoperable carcinoma of the breast. This group includes all types mentioned in Haagensen and Stout's classification. Here it is advisable to perform a simple mastectomy, to follow with deep X-ray therapy and to prepare for bilateral oophorectomy and adrenalectomy.

With the introduction of the concept of hormone-dependent tumours, the value of hormone treatment and oophorectomy, or oophorectomy plus adrenalectomy or hypophysectomy, must be considered in relation to the practical clinical problem.

Permission must always be obtained before operation that, if microscopy shows numerous mitotic figures, oophorectomy may be performed at the same time as mastectomy.

In all cases deep X-ray therapy should follow mastectomy. In the inoperable group there is possibly some advantage in pre-operative deep therapy followed by mastectomy and then bilateral adrenalectomy.

CASE REPORT

The features of this classification are illustrated in the following case report:

A European female aged 51 was seen on 15 December 1951 with a mass in the right breast, diagnosed as a stage-I carcinoma. Radical breast excision and clearance of the axilla was performed on 22 December 1951. The growth consisted of trabeculae of somewhat undifferentiated spheroidal cells. There was much pleomorphism with innumerable mitotic figures. There was a marked fibrous tissue response. The features were those of a carcinoma simplex of the breast of the so-called scirrhous type. Dissection of the breast and axillary contents revealed no further spread or metastatic growth.

She received X-ray therapy post-operatively and convalesced normally except that she continued to complain of hot flushes, present before the operation.

In December 1952 she began to complain of low back pain. X-rays revealed an extensive lesion of the 12th dorsal vertebra due to secondary deposits. X-ray therapy was given with some relief, but the pain returned and in June 1953 pain was continuous in the back, extending around the waist on the right side and down as far as the right calf. The menses ceased at this time. In June and July 1953, 1,000 mg. of Testosterone were administered by injection with alleviation of pain. Oral Testosterone was continued in smaller doses until September 1953, when there was

very little pain but hypertrichosis, coarsening of the skin, seborrhoea and deepening of the voice were pronounced. Heberden's nodes appeared in the fingers and Testosterone was discontinued. X-rays revealed new areas of infiltration in the pelvis, femoral heads and trochanters. X-ray therapy was applied to the affected areas. Intramuscular injections of Testosterone were resumed in October 1953 and the dosage gradually increased from 300 mg. to 750 mg. weekly. This therapy was continued until the pre-operative stage of her illness.

During the next 6 months she carried on normal household activities, appeared vigorous, although complaining of pain in the neck and shoulder, and in March 1954 complained of very severe pain in the left chest, restricting her breathing. X-rays revealed extensive deposits by secondary growth in the 4th, 7th, 9th and 10th ribs on the left side. X-ray therapy was resumed to these areas. Irgapyrin was given by injection and later Butazolidin orally, with apparent palliation. At this stage (March 1954) treatment was supplemented by oral administration of cortisone acetate, 100 mg. a day. This resulted in a better appetite and a feeling of well-being. In May and June 1954 she developed severe pain in the head, neck and shoulders and burning back pain. She found herself forced to lie down and rest most of the day; even talking was painful. X-rays in June 1954 showed multiple osteolytic metastases in the skull, cervical, dorsal and lumbar spine and pathological fracture of the 4th lumbar vertebra. There were secondaries in the scapulae, ribs and pelvis. No deposits were seen in the lungs. A persistent metallic taste which developed was bitterly complained of and led to the omission of cortisone by 22 June. Largactil and Pethidine were given for pain with no relief.

Bilateral adrenalectomy and oophorectomy were advised and accepted. Within a few days the patient was admitted to hospital in severe pain, vomiting food and fluids and unable to talk except in a whisper. She was unable to move her head, to sit up or turn. Examination showed no skin nodules, a normal left breast, no enlarged lymphatic glands, no enlargement of the liver and no physical signs in the lungs or heart. Blood pressure: 130/80 mm. Hg. Pre-operative and post-operative substitution treatment was carried out according to the method used by Pyrah and Smiddy,¹⁴ slightly modified.

Day before operation: Cortisone acetate, 50 mg. 6-hourly (intramuscular); Doca 5 mg. (intramuscular); sodium chloride 3 g. by mouth.

Day of operation: Cortisone acetate, 150 mg. 1 hour before operation and 50 mg. 4-hourly intramuscularly; Doca 5 mg. intramuscularly.

First post-operative day: Cortisone 50 mg. 6-hourly intramuscularly; Doca 5 mg. intramuscularly; sodium chloride 3 g. by mouth.

Days 2-6 post-operative: Cortisone 50 mg. 12-hourly by mouth; Doca 3 mg. intramuscularly; sodium chloride 3 g. by mouth.

After the 6th day: Cortisone 25 mg. 12-hourly; sodium chloride in excess of normal use.

Laboratory investigations carried out on admission (6 July) 1954 were as follows:

Full blood-count: Haemoglobin 18.3 gm.%, Red cells 6,260,000 per c.mm. Leucocytes 13,700 per c.mm. Polymorphonuclears 83%, with a shift to the left.

Serum calcium: 12.5 mg. per 100 c.c. (normal range 9-11 mg. per 100 c.c.).

Urinary sodium: 100 mg. per 100 c.c. (normal 670 mg. per 100 c.c.).

Urinary calcium: 14.3 mg. per 100 c.c. (normal 13 mg. per 100 c.c.).

Serum sodium: 315 mg. per 100 c.c. (normal range 325-350 mg. per 100 c.c.).

Total serum protein: 6 gm.% Serum albumin 3 gm.%; globulin 3 gm.%.

Blood alkaline phosphatase: 5.8 King-Armstrong units (normal 5-10).

Serum phosphorus: 3 mg. per 100 c.c. (normal range 2-4 mg. per 100 c.c.).

Blood urea: 80 mg. per 100 c.c.

Catheter urine: Contained no albumin, no sugar and scanty epithelial cells. There were numerous bacteria and a profuse growth of coliform bacilli was obtained on culture.

Intravenous fluid dextrose and saline were administered together with vitamins B and C. Vomiting ceased in 48 hours and

she ate normally. Gantrisin was given for the bacilluria and on 16 July the blood urea was 75 mg. per 100 c.c., urine culture showing only scanty organisms at this time.

Operation was performed on 19 July 1954. Hibernation anaesthesia was employed and the patient was placed flat on her back; through a mid-line lower abdominal incision the ovaries were removed.

The patient was then turned on her left side, the table depressed at the head and the feet, and the incision was marked out in a line from the umbilicus to the 10th thoracic spine, passing over the 12th rib, which was outlined. The incision was then made, passing from the lateral border of the rectus to about 4 inches from the 10th spine. The abdominal muscles were incised and the peritoneum separated from them and from the under surface of the 12th rib and diaphragm. The 12th rib was dissected free and disarticulated. The pleural reflection was visualized passing across the 12th rib and carefully preserved. The diaphragm was retracted superiorly and the peritoneum mobilized forward from the kidney. Through the peritoneum the liver and the portal vein could be seen. Posteriorly the kidney and its covering fascia (Gerota's fascia) were seen.

The adrenal gland, situated superior and medial to the kidney, was recognized by its yellow colour. After gentle dissection medial to the kidney, the inferior vena cava could be seen with the short branch of the adrenal vein passing to the gland. The removal of the gland was done by ligation of the vessels passing to the gland by means of an aneurysm needle, freeing the gland first medially and then superiorly and laterally. Finally the attachments through Gerota's fascia to the kidney were divided.

Haemostasis is not difficult if a gentle technique with ligation is used rather than artery forceps. Closure of the muscles in layers and skin suture were done without drainage.

The patient was then turned on the right side and the incision marked out in the same manner as before, the operative procedures being repeated on that side. The structures are slightly higher and the only difference is the sight of the spleen through the peritoneum instead of the liver.

There was no evidence of shock.

Microscopy of the ovaries and the adrenals did not reveal any pathology.

The decision about a 1-stage or 2-stage operation on the adrenals depends on the condition of the patient and whether the pleura has been left intact on the first side. It is a wise precaution to do only the one side if the pleura on that side is opened. Suturing of the thin pleura is always precarious and, in moving of the patient, it is easy to injure the suture line, resulting in an opening between the pleural and abdominal cavities with collapse of the lung. Moving the patient at the end of the bilateral operation, when the pleura has been opened, is always a hazard.

Post-operative Course. This was uneventful until the 30th day. For the first 2 days the patient was drowsy (owing to the hibernation anaesthesia) but in good condition and gave no cause for concern at any time. The blood pressure was maintained between 110 and 130 mm. Hg systolic without the use of Levophed.

The patient afterwards stated that during this period she felt herself struggling to live. These sensations were not apparent to us. On the 3rd day she stated that her pains were relieved. On the 31st post-operative day she suffered a bereavement. A close friend (who had lived with her for many years) died in her home. She developed vomiting and acute circulatory collapse with acute adrenal insufficiency after a period of severe emotional reaction with crying and exhaustion. The systolic blood-pressure fell to 80 mm. Hg. She responded rapidly, however, to intravenous saline and intramuscular cortisone, 100 mg. 6-hourly. On the 64th post-operative day there was an acute pain in the chest on the left side, with fever. There was diminished air-entry on the left side, with dullness but no haemoptysis. No phlebitis was apparent and the pain subsided in 4 days.

Progress has been satisfactory since then and there has been little or no pain. She requires no medication other than hydrocortone 20 mg. twice daily by mouth and goes about her usual household duties. She travels to town by bus when necessary.

Laboratory investigations carried out after operation were as follows:

Serum calcium, 20 July: 9.9 mg. per 100 c.c.

Blood urea, 22 July: 68 mg. per 100 c.c.; 11 August: 40 mg. per 100 c.c.

Serum sodium, 22 July: 315 mg. per 100 c.c.; 18 August: 320 mg. per 100 c.c.

Serum potassium, 22 August: 18 mg. per 100 c.c.

Urinary sodium, 22 July: 50 mg. per 100 c.c.

Urinary calcium, 29 July: 12.6 mg. per 100 c.c.

Blood alkaline phosphatase, 2 August: 29.2 King-Armstrong units.

X-ray examination on 18 November 1954 showed a very marked improvement in all the secondary deposits with recalcification. The secondary deposits were very much smaller in all lesions (Figs. 1-4). Dr. H. I. Osler reported as follows on the radiographs taken in August and November 1954:

Pelvis. A very marked improvement is seen in the deposits in the pelvic bones, and in the deposit in the right wing of the sacrum. The secondary deposits are smaller, and are recalcifying.

Lumbar Spine. The main comparisons (between the 12th dorsal and the 4th lumbar vertebral bodies) show a similar improvement. The 4th lumbar vertebral body is consolidating and recalcifying, and shows some deformity from compression. The 12th dorsal shows a slight irregularity of trabeculation, with no evidence of any compression.

Cervical Spine: The vertebral bodies show deformity, and the neck is rather short and thick, but no evidence of any active deposits can be demonstrated.

Skull: A very marked improvement in the secondary deposits is demonstrated. They are smaller and are recalcifying, and no radiological evidence of intracranial pressure is seen.

There is a very marked improvement in all the secondary deposits, with recalcification; the secondary deposits are very much smaller in all the lesions.

DISCUSSION

Modern endocrine therapy of breast cancer is based on research associating oestrogens with the development of breast carcinoma in experimental animals. This knowledge we owe to the work of Loeb,¹⁷ Murray¹⁸ and Lacassagne.¹⁹

Out of this arose the concept of hormone-dependent tumours,²⁰ including cancers of the breast in men and women. Hadfield²⁰ gives an excellent review of the subject of so-called hormone-dependent carcinomata. The rationale of the hormone treatment of carcinoma is considered as well as the different problems before and after the menopause. He describes the spontaneous carcinoma which arises in hybrid mice, develops during pregnancy and disappears when the pregnancy is over, but is re-activated with further pregnancy. He points out that the small terminal ductules of the breast are the cells particularly sensitive to oestrogen.

Endometrial studies of women in the post-menopausal period show that 30% continue to produce endogenous oestrogen. This is confirmed by vaginal smears. The probable source of these oestrogens is the adrenal cortex. Nevertheless, prolongation of life by hormone treatment must be assessed against a background of the natural history of untreated mammary carcinoma. Gordon-Taylor²¹ reports an average duration of survival, untreated, of 25.4 months in the cellular type and 5½ years in the scirrhous type, with an over-all average of 3½ years. Riddell² reported that the average natural duration of life of the untreated breast carcinoma was 3½ years. Loeser²³ and Adair and Herman²⁴ treated breast cancer with testosterone and found regression of the primary tumour as well as of osseous secondary deposits. Raven,²⁵ treating breast cancer and osseous metastases with methyl testosterone, has described survival in 2 cases for periods respectively of 6 and 7



Fig. 1. X-ray of pelvis on 6 July 1954.



Fig. 2. X-ray of pelvis on 16 November 1954.



Fig. 3. X-ray of skull on 20 September 1954.

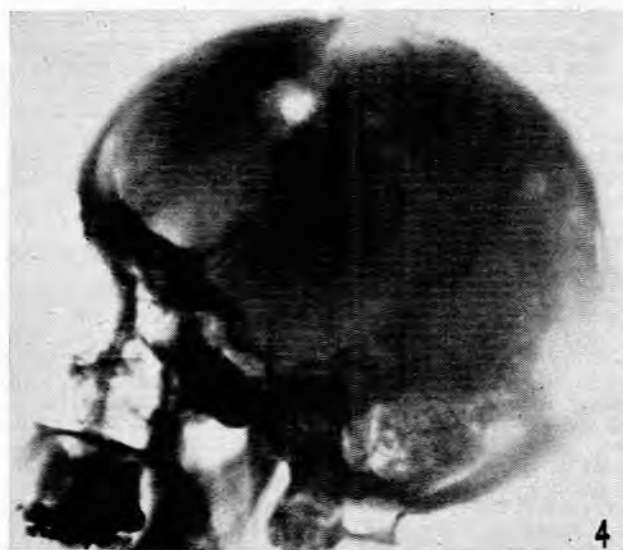


Fig. 4. X-ray of skull on 16 November 1954.

years after commencing therapy. Apparently some of these patients are sensitive to variation of their sex-hormone balance, for regression of the disease may be achieved by the administration of oestrogen or androgen, and by oophorectomy or adrenalectomy or both operations combined. Possibly gonadal hormones act by depressing excessive production of pituitary tropins, such as may occur after the menopause.

However, it is advisable not to administer oestrogen to pre-menopausal women, for breast cancer may be stimulated. Its use should be restricted to patients well past the menopause. Such treatment should be combined with X-ray therapy. Androgens may be used in the younger age-group. The primary growth, soft-tissue lesions, and glandular, osseous and other metastases, may all regress, even to the point of complete healing.

Oestrogens have a greater effect on soft-tissue lesions and androgens on bony metastases.

Oophorectomy leading to clinical improvement in breast cancer was first recorded by Beatson²⁶ in 1896, and Lett²⁷ in 1905 collected 99 such cases. In 23% of these there was much improvement. The operation has been re-introduced in recent years. X-ray irradiation of the ovaries has also been used. Raven²⁵ reported a case of breast carcinoma with cervical and lymph-node metastases alive and well with no signs of cancer 5½ years after oophorectomy.

Huggins and Dao,²⁸ acting on the assumption that renewed growth of hormone-dependent tumours after oophorectomy is due to the elaboration of steroids by the adrenal cortex, were able to induce a further regression in cases of human mammary and prostatic

cancer by performing bilateral adrenalectomy and maintaining the patient on cortisone acetate. They reported on 55 cases, including 2 men and 53 women, with mammary carcinoma treated by adrenalectomy. Fifty of these cases are reviewed; 25 patients aged 44-70 years had adrenalectomy alone and 25 patients aged 29-59 years had oophorectomy with bilateral adrenalectomy. Ten patients in each group, with regression and metastases in bones and pleura, showed the best results, with recalcification of osteolytic secondaries and disappearance of intrathoracic deposits on X-ray.

Cade²⁹ reported 46 adrenalectomies in 1954 for breast cancer and assessed the results as 23.7% with remarkable, dramatic and in many ways surprising improvement; 31.6% showed satisfactory improvement, with relief of pain not quite complete and new lesions appearing while existing ones faded away; 38.9% showed no subjective or objective improvement.

On the assumption that oestrogenic activity of the adrenal gland is due to pituitary tropin, Luft and Olivecrona³⁰ performed hypophysectomy in 9 cases with 'huge recurrences' after mastectomy in breast cancer. In one case where removal was complete, as shown by tests of pituitary function, healing of the enormous, ulcerated, cancer surface occurred in 8 months and the biopsy examinations at intervals showed gradual disappearance of carcinoma cells, just as has been noted in cases treated by adrenalectomy. Five cases are too recent for assessment, and in 2 cases with no improvement tests showed functioning pituitary tissue. One case died 3 months after removal of the pituitary without improvement. They consider the operation in these cases to be comparatively free of danger and well tolerated.

Perrault³¹ describes improvement 2 years after hypophysectomy for cancer of the breast with metastases. He mentions the ease of correction of thyroid and adrenal cortical deficiency after operation but warns against the too ready use of cortisone, which may reactivate hypophyseal tissue left behind at operation.

The case reported here is of interest because of the severity of the clinical symptoms. She was bedridden and riddled with osseous metastases. The high blood-urea may have been due to the hypercalcaemia causing renal damage. Nephrocalcinosis was considered but no evidence of this was seen on X-ray.

In spite of this, bilateral oophorectomy and adrenalectomy were performed in one stage, with relief of pain in 72 hours, recovery of the patient to a state of normal activity up to the time of writing, and recent radiological evidence of healing of osseous metastases, 4½ months after the operation.

Attention is drawn to an acute Addisonian crisis which resulted from a severe emotional upset during convalescence, and was readily corrected by increasing the dosage of cortisone. Hydrocortone substitution therapy has been shown not to be associated with disturbance in taste in her case.

Hypocalcaemia and hypercalcaemia pre-operatively were considered to be due to bone destruction from osteolytic bone deposits.³² Reversal of this post-operatively was taken to indicate cessation of the activity of the cancer deposits. Increased blood alkaline phosphatase post-operatively was an index of improve-

ment indicating osteoblastic activity and healing.

The virilizing effect of androgen therapy has now disappeared.

The microscopic appearance of the primary growth (an undifferentiated carcinoma) did not encourage us to expect so favourable a response. Huggins and Dao²⁸ and Pyrah and Smiddy¹⁶ agree that tumours with an alveolar structure respond most favourably to adrenalectomy.

SUMMARY

1. The orthodox surgical treatment of breast cancer is reviewed critically and a new method of staging is described, significant in deciding on surgical endocrine procedures, e.g. oophorectomy with or without adrenalectomy.

2. A case of breast carcinoma with osseous metastases improving dramatically with healing of bone lesions after bilateral oophorectomy and adrenalectomy is described.

3. The primary growth was an undifferentiated carcinoma, a type regarded by some authors as less amenable to this form of treatment.

4. The progress and rationale of endocrine therapy is discussed and reference is made to hypophysectomy in the treatment of breast carcinoma.

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