

RES MEDICA

Journal of the Royal Medical Society



Modern Concepts of Breast Carcinoma

Sir Arthur Porritt

K.C.M.G., C.B.E., M.A., M.Ch., F.R.C.S.

Sergeant Surgeon to H.M. the Queen

Abstract

Twenty years ago, it was generally considered that breast cancer was readily accessible to radical surgery and that radical surgery had more to offer here than perhaps anywhere else in the body. In the intervening years, this pseudo-complacency has suffered a series of rude shocks, until to-day the pendulum has swung full distance and radical mastectomy plays but a minor role in the treatment of carcinoma of the breast. The now obvious gaps in our armamentarium have been filled by X-ray therapy, with or without local surgery, by the use of the sex endocrines and the cortico-steroids and by what may be termed "physiological" operations on various endocrine glands.

Copyright Royal Medical Society. All rights reserved. The copyright is retained by the author and the Royal Medical Society, except where explicitly otherwise stated. Scans have been produced by the Digital Imaging Unit at Edinburgh University Library. Res Medica is supported by the University of Edinburgh's Journal Hosting Service: <http://journals.ed.ac.uk>

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

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

Res Medica, Winter 1957, 1(1): 20-31

[doi:10.2218/resmedica.v1i1.288](https://doi.org/10.2218/resmedica.v1i1.288)

MODERN CONCEPTS OF BREAST CARCINOMA

By SIR ARTHUR PORRITT

K.C.M.G., C.B.E., M.A., M.Ch., F.R.C.S.

Sergeant Surgeon to H.M. the Queen

TWENTY YEARS AGO, it was generally considered that breast cancer was readily accessible to radical surgery and that radical surgery had more to offer here than perhaps anywhere else in the body. In the intervening years, this pseudo-complacency has suffered a series of rude shocks, until to-day the pendulum has swung full distance and radical mastectomy plays but a minor role in the treatment of carcinoma of the breast. The now obvious gaps in our armamentarium have been filled by X-ray therapy, with or without local surgery, by the use of the sex endocrines and the cortico-steroids and by what may be termed "physiological" operations on various endocrine glands.

In the mid-thirties, the surgeon could accept full responsibility for treatment by the use of his technical skill. Nowadays, however, each individual patient, and almost each individual cancer, demands such nicety of judgment and keenness of assessment, if the correct method or combination of methods is to be used, that the surgeon must enlist the co-operation of those of his colleagues who specialise in radiotherapy, in histo-pathology and in steroid chemistry.

The complexity of the subject of breast cancer therapy is now all too obvious and many of us feel we are groping in a very stimulating but very perplexing dark. Hence, there may be some value in a general surgeon, who can contribute little new to the problem, attempting a summary of the existing situation.

Such is the breadth of knowledge now required and so great is the accumulation of new facts and theories concerned that even my thirty years of clinical experience seem an indifferent qualification for the task. Such experience, however, does indelibly impress upon one's mind and on one's heart that breasts belong to people! And these people, our patients, are well aware not only of the dual functions of the breast for lactation and decoration, but also of the sword of Damocles that hangs over them in the sinister shape of carcinoma. I do not intend to enlarge upon this aspect save to stress the vital importance to the patient of undergoing any form of treatment which may involve disfigurement or mutilation. Many patients will state, quite honestly, that they would prefer to keep their carcinoma rather than submit to radical mastectomy.

The breast is so readily accessible to the patient, and she is usually so well aware, either subjectively or in fact, of pathological changes in it, that in no sphere of clinical surgery can that much-maligned phrase "the doctor-patient relationship" be more profitably exercised or the milk of human kindness be more sympathetically expended.

May I first consider briefly some points relative to the history, incidence, aetiology, clinical picture and prognosis of the disease?

History

From the detailed description of what he termed "Bulging tumours of the Breast," it would seem that the great Egyptian surgeon of 3000 B.C., Imhotep, recognised breast carcinoma as an entity. His findings are recorded in the Edwin Smith Surgical Papyrus and probably constitute the first written word on this dire disease. Hippocrates was well aware of it and enunciated the odd theory that bleeding from the nipple was a sign of madness. Celsus, in 100 B.C., advocated the treatment of mammary carcinoma by caustics; this method retained its popularity for centuries and was, amazingly enough, used in this country as recently as the 1860's. Sir D'Arcy Power recalled having seen two cases so treated in his youth and I believe these two specimens are still to be seen in the museum of St Bartholomew's Hospital. Neither must we forget the name of Galen in this connection, for it was he who likened the disease to a crab and thus gave it the name which has lasted to this day. From descriptions in medieval literature, it would seem that only very advanced and usually fungating, cancers came to light and these were treated surgically by operations, deservedly labelled "amputations." Many illustrations in ancient books can still be found showing a weird variety of slices, shears and clamps used for this purpose, and the accompanying rope tied round the base of the breast as a form of tourniquet was a well-known feature.

The first form of planned mastectomy was probably carried out by Jean Petit in the early seventeenth century, but more than a hundred years had still to pass before we come to the great pioneers of breast surgery, to whom we should surely pay homage, Charles Moore, Mitchell Banks, Sampson Handley and Cheate in this country, and Pancoast, Samuel Gross and Halsted in America. All these men worked on the hypothesis that to eradicate breast carcinoma, as well as the tumour itself, all areas of lymphatic drainage that were surgically accessible should be cleared. Charles Moore, of the Middlesex Hospital, first practised the removal of the pectoral muscles and their accompanying lymphatic chains in 1867. Some ten years later, Mitchell Banks of Liverpool described his axillary clearance and, in 1889, Halsted of Baltimore introduced a radical mastectomy which is still the prototype of all radical mastectomies done to-day. This is surely a wonderful tribute both to the man and his method. Re-orientation of our ideas on this subject has served only to limit the scope of the operation and not to decry its technique or rationale.

Incidence

I have already used the words "dire disease" and this carcinoma of the breast most certainly is. Statistical evidence seems to show quite definitely that, even allowing for a slow increase in the average age of the population, its incidence has specifically increased in the last thirty years. It accounts for approximately one-third of all malignant neoplasms in women; one woman in every twenty of adult age acquires it; it kills over 7000 women every year in this country. But, unlike certain other growths, it flourishes in almost every clime and every quarter of the globe, and now has the sinister reputation of having outstripped its partner in crime, carcinoma of the uterus, as the most lethal carcinoma in women.

Its peak incidence is certainly in the menopausal years, particularly when this period is either delayed or protracted. The rather futile controversy as to which breast is the more frequently attacked still goes on, but the stress laid of recent years on endocrine influence gives more point

to the equally debated question as to whether the breast that has lactated is more likely to develop cancer than the virginal breast or vice versa.

Aetiology

In respect of aetiology, carcinoma of the breast differs little from its fellows elsewhere in the body. Theories are rampant, facts are few. Bittner's discovery of his "milk factor" in 1936 stimulated a genetic approach. The action of this virus-like agent, transmitting dominantly through the female mammary tumors to suckling mice and, at the same time, producing anti-carcinogenic antibodies, has unfortunately never been established in the human. But few will deny that a familial trend exists not only towards carcinoma in general but more specifically to carcinoma of the breast itself. Jacobson of Denmark, some ten years ago, however, favoured the theory of a general cancer gene, transmitted according to Mendelian principles and estimated by him to be present in approximately 10% of the population. Only much time, together with detailed statistical work, could prove or disprove this conception. Whether such a genetic or familial trend does or does not exist, there is no doubt that the factor of chronic irritation is a potent one in breast carcinoma. It has been truly said that carcinoma of the breast thrives in an environment of oestrogens, a fact which almost certainly accounts for its marked predominance in women and probably also for the fulminating characteristics of pregnancy carcinoma, when the placenta adds its considerable quota of oestrogens to those already present. Throughout a woman's functional life, the breast responds in varying degree to a repeated cyclical stimulation from oestrogens which leads in a proportion of patients, to the cystic degeneration of fibro-adenosis. Again, the stagnant secretions of the breast, particularly after lactation, have been indicted as potential irritants. Yet one more thought is perhaps worthy of consideration in this respect: two out of every three carcinomata of the breast occur in the outer quadrants. The difference in tissue mass as represented by the axillary tail is so small that the probability of multiple minor traumata should perhaps be entertained. In other tissue, the carcinogenic significance of repeated trauma is well enough established.

Clinical Picture

No detailed description of the clinical picture is called for in this lecture but perhaps one or two salient points merit attention. The controversial question of "staging" still awaits solution. The fallacies of clinical staging become more obvious every day, even admitting a certain degree of international unanimity in definition of the various stages. Surgical or operative staging, pathological staging and histological staging, all show how erroneous the first clinical assessment can be. Axillary glands, the crucial factor in correlating clinical findings to therapy, are clinically missed in as many as 50% of cases and, when found, by no means always harbour metastases. Add to this the findings of Sampson Handley and Scarff, that one-third of all cases and 50% of inner quadrant cases produce clinically undiscoverable internal mammary and mediastinal glands and the value of clinical staging, except for preliminary descriptive purposes, seems to get smaller and smaller.

The importance of the doubtful lump, however, becomes greater as the education of the lay public extends. If every doubtful lump in the

breast were discovered, reported and dealt with whilst still covered by that label, the figures for carcinoma of the breast would undergo a magical transformation. I still like to use, both to patient and student, those three excellent aphorisms of Riddell—

“The period of observation is the period of lost opportunity”;

“No lady keeps a lump in her breast”; and

“Beware the ample bosom.”

The clinical diagnosis of carcinoma of the breast is not as easy as the text-books used to lead us to believe. The doubtful lump is far commoner than the classical carcinoma and it is the former that will produce therapeutic dividends. After all, it is the survival of the patient that counts.

In this connection, one must always bear in mind the fact, which is now well established, that the average span of life in untreated carcinoma of the breast is three years. Hence, figures of three years' survival *after* treatment are relatively worthless. It seems obvious that the disease runs a natural course, that there are certain factors which expedite that course and others which delay it, some almost indefinitely. In treatment, we break into the natural course for better or for worse, and it needs the keenest judgment to decide if and how, and where, to make that break.

Prognosis

Carcinoma of the breast, being so readily accessible clinically, affords numerous examples of what Gordon-Taylor has described as “cancer immunity.” The atrophic scirrhus of the eighty-year-old patient which she has knowingly kept for twenty or thirty years is a classical example. In prognosis, the rate of growth is infinitely more important than the duration of symptoms. The lethal encephaloid cancer often kills the patient without producing a single metastasis. Again, quite frequently, long intervals of many years may transpire before secondary growths, which must presumably have been in situ before the primary was removed, effloresce into further and very fatal activity. This represents a breakdown in immunity and such a failure of the natural mechanism is usually a concomitant of other quiet unrelated illnesses. These happenings, and even the well-authenticated actual disappearance of some tumours, all offer very intriguing problems which are probably associated more with the aetiology of cancer as a whole rather than of the breast in particular.

Age is undoubtedly a factor in prognosis and, despite the widely held belief that the younger the patient the worse the outlook, Macdonald has recently produced figures to show that the immediate post-menopausal years (50-60 age group) are probably the most dangerous. It has only recently become appreciated that, at this stage, oestrogen production is not as deficient as was formerly thought.

Before delving deeper into a consideration of methods of treatment to-day, I feel I should list the series of jolts which personally destroyed my complacency in the belief in which I had been brought up, that for all cases of breast carcinoma, which were not obviously hopeless and moribund, the answer was radical mastectomy. They were:

- (i) Thoughts about the hormone dependency of carcinoma of the prostate and the fact that oestrogen therapy in man had produced carcinoma of the breast.
- (ii) The summary from St Bartholomew's Hospital, produced by Murley and his colleagues, showing that, over a period of ten

years, the results of treatment (irrespective of surgeon and and irrespective of method) showed a miserable 1% difference in survival rates.

- (iii) The work of Sampson-Handley (1952) on the frequency of lymphatic spread of growth to the internal mammary and mediastinal glands.
- (iv) The great advances in endocrine chemistry and their application to the problem of breast carcinoma, by surgery of the various endocrine glands and by sex hormone and steroid administration.

These developments seemed logically to push the pendulum of therapy further and further away from the radical surgery of the preceding sixty years. To-day, it would almost appear we have come to the point where, not only has the field of local surgery, that is surgery of the breast itself, dwindled to minor proportions, but where we must honestly face up to the question as to whether surgical therapy is indicated at all.

I feel one has only to ask this question to get at least a qualified affirmative but to decide into which class any particular growth, and any particular patient, falls is a matter of infinite difficulty. Even when one decides that treatment is indicated, which will obviously still be the case in the majority until our knowledge expands yet further, we now possess a great series of therapeutic weapons, besides mere local cutting, and their use, alone or in combination, requires almost the judgment of a Solomon.

Treatment

THIS may be very simply summarised as follows :

I SURGERY	{ Ultra-radical Radical Palliative	} with or Deep X-ray without Therapy
II RADIOTHERAPY	{ Alone Pre-operative Post-operative	
III HORMONE THERAPY	{ Oestrogens Androgens Cortisone	
IV ENDOCRINE SURGERY	{ Oophorectomy Adrenalectomy Hypophysectomy	
V SYMPTOMATIC		

It is obviously not easy to get all these various methods into perspective and it may be profitable first to discuss each as an entity and then to try and link them in combinations likely to give the best therapeutic results to each individual growth and patient. It will be immediately apparent, however, that surgery on the breast alone has but a limited scope. And that, to my mind, poses the first major question to be answered—"What now is the field of radical surgery?"

RADICAL SURGERY.—Unless, with all the knowledge we now possess and all the data we can accumulate in any particular case, we can honestly expect to extirpate the disease, lock, stock and barrel, then there is no excuse for the major mutilation involved. This is not the place to enlarge on the psychological effects of removal of the breast, but it is most certainly a matter that must be constantly in the forefront of our minds. Very few women can completely readjust mentally to the loss of a breast, valiant though their efforts may be. The absence of such an obvious physical

feature is a constant reminder of the sword of Damocles that has hung, and for all they know or are told, still hangs over them. The hiatus engenders almost as much, and sometimes more, mental trauma than did the original lump in the breast. This all-important fact and the accumulation of statistics of survival periods over now a long period of years, have given a new orientation to the value of radical mastectomy. There is no doubt, however, that the Halsted operation, which as a technical exercise has most certainly worthily stood the test of time and has now a world mortality of under 1%, can, in well-chosen cases, effect something as near a cure of breast cancer as anything we know. The choice—to mutilate or not to mutilate—depends essentially on the clinical presence of glands, apparent or presumed. There are those who believe that the lymphatic nodes, on the analogy of infection, are effective blocks in the path of spread and that to remove them by surgical dissection is deliberately to break down natural barriers. Professor McWhirter and his School here in Edinburgh, are the great protagonists of this belief, and it would certainly seem that figures amply bear out their hypothesis. In other words, nodes, unless minimal, are a contra-indication to radical surgery for they indicate a spread of the disease beyond the scope of surgical extirpation.

Therefore, the Halsted type of mastectomy should be limited to the case which is genuinely clinical Stage I—a lump in the breast with no clinical axillary glands. To this, one must add Sampson Handley's findings in respect of internal mammary gland involvement, which would logically limit the cases suitable for radical mastectomy to Stage I growths *in the two outer quadrants only*. In such cases, one may reasonably expect a five-year-survival rate of 80% and a ten-year-survival rate of 60-65% and these figures undoubtedly justify the mutilation involved. In this connection, it may be mentioned that adjuvant radiotherapy seems to effect no improvement in these figures and, therefore, it can fairly be said that, in this very limited field, surgery, and surgery alone, still offers optimum results.

It must be mentioned, however, that there is a small, but active school which sees in the new developments a challenge to surgery and which has extended the scope of the radical operation to include the removal of even wider fields of possible spread. Urban, in 1954, advocated and practised such an ablation which consisted of the lateral third of the sternum, the costal cartilages, the internal mammary vessels and their concurrent lymphatic chains and the supraclavicular glands and, of course, a full axillary clearance in addition. To a modified degree, Sampson Handley has extended the scope of the original radical mastectomy and it is not without historical interest to remember that Halsted himself, in his earlier days, included the homo-lateral supraclavicular glands in the scope of his dissections. Such heroic extirpations as Urban's must, of necessity, add to the morbidity and mortality of the operation and it remains to be seen whether ends will justify means.

PALLIATIVE SURGERY.—Going to the other extreme, once one has admitted the limitation of a radical operation and has frankly faced up to the fact that, in a particular case, the main therapeutic attack is not to be operative, there still remains a large and useful field of minor or palliative breast surgery. Professor McWhirter's contention that a removal of breast disc alone, together with X-ray therapy to control local recurrences, is better than radical mastectomy, is amply borne out by his figures which, to date, show an over-all 5% advantage for the simpler

methods and this figure has deservedly received world-wide attention. His results have been even better in Stage II growths than in Stage I growths and constitute a very definite advance in surgical thought on this most difficult problem.

If there is anything original I can personally offer in this question, it is work along similar lines which I began with the help of my radiotherapeutic colleague, Dr M. Hulbert at St Mary's Hospital some seven years ago. We have been even more conservative than McWhirter and have worked on the basis that, if surgery is not meant to be the main line of defence, it should not mutilate; I have removed simply the lump itself and a wedge of surrounding breast tissue and left the disc in situ. This has been combined in most cases with a very modified exposure of the axilla to prove or confute clinical findings in respect of axillary nodes and to obtain a suitable gland for biopsy and prognosis purposes. Each case has received adequate radiotherapy to those areas suggested as necessary by the clinical and surgical findings. Results to date are not sufficiently numerous to be statistically significant but the trend is quite obvious and follows exactly that of Professor McWhirter, showing a small but definite advantage in favour of the minor procedure in comparison to a parallel series of radical mastectomies. Moreover, there is the added advantage of a series of very grateful patients who have *not lost their breasts*.

I need not here do more than mention the obvious value of palliative surgery in dealing with the breast carcinoma that is about to fungate or has, in fact, fungated through the skin, though this again is a field where radiotherapy can be of the greatest use.

RADIOTHERAPY.—If we general surgeons are completely honest with ourselves, I think we regard X-ray therapy with an odd mixture of awe, doubt and respect! We have all seen the great relief it can give to frankly inoperable cases, both at the site of the growth and elsewhere; we have all frankly admired it for turning an inoperable case into an operable one, and we have all used it in the fond belief that it would be wrong not to twang every string in the therapeutic bow, however little we may know of its friability or its strength.

But the days when radiotherapy was looked on as the hand-maiden of mastectomy are past. It is an accurate and scientific therapeutic method in its own right and can be used as the sole method of treatment in certain selected cases of breast carcinoma. Its position in the therapeutic armamentarium can be likened to that of a Dominion in the Commonwealth; it has a domestic sphere of influence of its own and unites with the other "Dominions" of endocrine therapy and endocrine surgery to assist the "Mother Country" of General Surgery in an all-out attack in time of danger.

The potency and accuracy of radiotherapy have greatly increased over recent years with the arrival on the scene of the megavolt machine, the linear accelerator and the cobalt units. There would now seem no vestige of doubt that ray therapy can inhibit and even completely destroy neoplastic activity, and achieve this without mutilation and without mortality. Where to draw the dividing line between inhibition and destruction, with reference to the effect on normal tissues, is still a matter of debate. Many examples have been given of active cancer cells found locked up in the firm fibrosis of a gland treated by deep X-ray therapy. The dosage lethal to neoplastic cells lies very near, if not beyond, the tolerance dose of normal skin. Breast tissue, on the other hand, is of relatively low susceptibility. If

recurrences do occur after radiotherapy, they are notoriously resistant to further treatment. On the debit side of the balance, too, must be placed the quite definite, though admittedly temporary, physical discomfort, mental lethargy and depression which commonly accompany this form of therapy.

In using irradiation, just as much sound judgment and keen clinical and pathological assessment of a particular case are required as when surgical measures are contemplated. There are undoubtedly some cases which are resistant to radiotherapy from the start and, if it is given to such cases, spread seems to be accelerated and the actual areas treated tend to harbour metastases.

If used in conjunction with surgery, as is nowadays almost a routine, except perhaps for the genuine Stage I growth in the outer quadrants, its sphere can at first be limited according to glandular involvement, either surgical or pathological. It is wise, after operation, to leave sufficient interval to ensure good wound healing before starting treatment. Indifferent wound healing is one of the chief arguments, though not really a very cogent one, against pre-operative irradiation, as such treatment has a negligible effect on the technique of subsequent surgery.

Irradiation therapy produces its optimal effects in clinical Stages II and III. To give some idea of its value, the following average figures of a number of series may be quoted. In Stage II, the 10-year survival rate with surgery alone amounts to 25% only; if deep X-ray therapy has also been used, this figure is increased to 32%. In Stage III, surgery alone can claim only a 7% ten-year survival rate; surgery *and* irradiation, 9%, and radiotherapy alone 13%. In the later stages of the disease, when widespread dissemination has occurred, radiotherapy finds its greatest value in the relief of pain due to osseous deposits.

Before leaving the subject of irradiation, mention should perhaps be made of Pannett's recent intriguing suggestion that the benefit derived from ray therapy comes not from the direct effect on the cancer cell but from chemical changes produced in the surrounding normal cells, which are stimulated to produce chemical substances lethal to the neoplastic cell contained in their midst. This work derives from the original observations of Keynes in the early thirties, when he reported the disappearance of breast cancers surrounded by a ring of radium needles, a method similar to that used in the treatment of cancer of the tongue.

In introducing the next group of therapeutic measures available in treating breast carcinoma, it must be stressed that they have a value only in the so-called "hormone-dependent" growths which regrettably make up only some 45% at the most of all breast cancers. For the remainder, surgery and irradiation offer all that is available. But, for this 45%, if they can be identified, the field of therapy has, of recent years, expanded in a most dramatic manner. Heretofore, this identification has been by trial and error and the whole subject has been on a purely empirical basis. Only after protracted courses of hormone therapy or having undergone major operations on the endocrine glands, could the unfortunate patient be told that her growth was not hormone dependent. Histological examination of the tumor often gives a good lead in making a decision on dependency for the greater the cellular differentiation of the growth, the greater the likelihood of its being dependent. Again, the age of the patient was assumed to be a reasonable pointer. The younger patients produce a much higher proportion of dependent tumours because their oestrogen output is relatively so much greater. Even now, doubt

is being cast on the oestrogens as the only hormone involved, and the work of Skowen and Hadfield recently stresses the importance of pituitary prolactin as a potent force. From their research, the possibility of a breast cancer stimulated entirely by a pituitary hormone certainly cannot be ruled out and proof is more than presumptive that, even if this is not so, the pituitary and ovarian hormones are synergistic in their influence on mammary carcinoma.

To-day, however, it is possible, by a number of bio-assays, chemical estimations and clinical tests, to *prove* that a particular growth is hormone-dependent. We have passed from the empirical state of qualitative endocrinology to the quantitative. Certain laboratory estimations and assays have now been developed which make possible two clinical tests that go a long way to prove the hormone dependency or otherwise of any given tumour.

In the blood, a raised serum calcium and a raised alkaline phosphatase are both indications of the likelihood of osseous metastases, whilst a raised acid phosphatase points more to visceral secondary deposits. Calcium excretion in the urine is a good index of bone destruction and can be estimated quantitatively. As a round guide, it can be said that every 100 mg. of urinary calcium represent 1 g. loss of skeletal bone.

The endocrine assays are a more recent development. F.S.H. estimations show indirectly the patient's oestrogen activity, and it is well to remember that the more oestrogens the more growth. Since oestrogens inhibit the pituitary, the more F.S.H. the less oestrogen.

By the bio-assay method of Allen and Doisy, however, it is now possible to estimate oestrogen levels directly and to divide them into their "To" and "Tzn" fractions. After a normal menopause, F.S.H. values are high, but in cases of cortical stromal hyperplasia, an opposite trend is noticed and oestrogen values, especially of the "Tzn" fraction, rise sometimes to phenomenal heights, especially in cases of breast carcinoma. Hadfield's urinary assays of mammatrophic hormones in the urine have provided a most useful guide to the potential value of hypophysectomy.

The two clinical tests which can be applied to any patient with breast carcinoma and particularly those in the advanced stage, where hormone therapy or endocrine surgery is being contemplated, are as follows:

1. The Stilboestrol Stimulation Test is self-explanatory. The exhibition of stilboestrol produces both a raised serum calcium and a raised urine calcium excretion, together with an obvious worsening of symptoms, especially pain, in any patient whose growth is hormone-dependent. The trial dose of stilboestrol is usually 10 mg. daily for three days, and the effects of this in a susceptible case may last for as long as a month. The test should not be used in patients with poor renal function. It is hardly necessary to say that the raised calcium figures will apply only to cases with osseous metastases.

2. Cortisone Inhibition Test: Here, the effect is just the opposite and, together with amelioration of clinical symptoms, there is a marked fall in urinary calcium excretion. The usual dose of cortisone given is 200 mg. daily for three days, followed by 100 mg. daily for as long as required.

Without previous oophorectomy, the test, of course, loses its value.

One may now, perhaps, say a few words about the specific uses of the several hormones used in therapy and the operations performed to regulate their activity.

Hormone Therapy

Oestrogens : Stilboestrol (usually prescribed in the form of dinoestrol) finds its chief use in the treatment of the elderly patient. In such a case where the natural supply of oestrogens has dried up, stilboestrol, probably by acting as a pituitary depressant, actually inhibits the growth which, in an earlier age group, it would have stimulated. It is this latter fact which underlines the danger of the rather wholesale prescribing of stilboestrol for the pains of fibro-adenosis that is so prevalent to-day.

In general, therefore, stilboestrol should not be used before the menopause, nor is it wise to use it in cases where there is a family history of carcinoma, or where the disease presents with bleeding from the nipple. Beneficial effects are best shown on visceral metastases, but side-effects are not uncommon, particularly subcutaneous oedema due to salt and water retention, pain in the breast, uterine bleeding and nausea. In those cases which react favourably, about 40% of visceral metastases and 30% of osseous, the remission can be expected to last up to two years or more.

Androgens are usually given in the form of testosterone propionate, and are chiefly used in the pre-menopausal patient. Such temporary remission of symptoms as they produce, especially of pain in the case of osseous secondaries and in the late exacerbations following adrenalectomy, occur in not much more than 20% of cases and rarely does the improvement last more than a year. Side effects of masculinisation are common. It would probably be fair to say that the androgens never produce such a good effect as oophorectomy, but they can be used after this operation with advantage, to enhance the effect.

Cortisone : Steroid medication inhibits both adrenal and pituitary function and it is most important to bear this fact in mind when assessing the results of adrenalectomy. After this operation the administration of cortisone becomes essential and it seems not improbable that the apparently beneficial effects of adrenalectomy are, in fact, due directly to the replacement doses of cortisone and not to the adrenal ablation. Adrenalectomy is known to produce a marked increase in both ACTH and mammatrophic hormones and, therefore, it is possible, in tumours which are pituitary-dependent, that adrenalectomy may, in fact, do harm that will automatically be corrected by the subsequent giving of cortisone. It is believed, by some workers, that cortisone has a direct action in that it competes with oestrogen for protein molecules in the circulating blood and, as the oestrogens have the greater affinity, very large doses of cortisone are required to displace them. Hence the possibility of ultimate "escape" from cortisone effect when the dosage becomes so heavy as to produce such well-marked side-effects as "moon-face" and peptic ulceration. Such an "escape" usually occurs within a two-year period from the start of cortisone therapy. To-day, cortisone is most frequently exhibited in the form of prednisone, which has less tendency to lead to distressing side-effects.

Endocrine Surgery

In considering endocrine surgery, what has been so forcibly termed elsewhere "a series of planned rearguard actions" implies that the battle has been already lost and one is only "staving off" the inevitable. But it is also fair to say that the three operations of oophorectomy, adrena-

lectomy and hypophysectomy have given months, and even years, of life with great improvement of symptoms, to cases which must otherwise have perished out of hand. At the risk of being repetitive, it must be stressed again that good can be done only in those cases in which the growth is hormone-dependent and that these number less than 50% of the total.

OOPHORECTOMY.—This was practised empirically for cases of breast carcinoma as long ago as 1896. It probably fell into disrepute because, at that time, it was not appreciated that its possible sphere of usefulness was so limited and, if *all* cases were treated by ovarian ablation, the results would certainly not recommend the operation.

Its possible value would seem to be greatest obviously where urinary oestrogen values are highest, that is in pre-menopausal patients particularly and, to a lesser extent, in menopausal cases which form a relatively large group, and in those post-menopausal women who have cortical stromal hyperplasia of the ovaries. In passing, it should be noted that breast carcinoma has been reported to occur in 2% of previously castrated women.

Regarding the method of producing castration, there seems to-day a consensus of opinion that surgical removal gives a definitely more complete and effective result than irradiation.

ADRENALECTOMY must be combined with, or follow, oophorectomy if it is to achieve beneficial results in the treatment of advanced hormone-dependent breast cancer. In such cases, which can now be identified by a good response to the cortisone inhibition test, the remaining oestrogen factory producing mainly the "Tzn" fraction, is removed. The operation has small value where the metastases are hepatic, cerebral or pulmonary, but osseous deposits particularly and, to a lesser extent, skin secondaries, are favourably affected. The leading protagonist of the operation in this country, Stanford Cade, claims approximately 100% satisfactory remissions in castrated women, one-third of these being benefited for periods of two years or more. The best results appear to occur in those cases where the original breast growth was *not* a scirrhus carcinoma. However, the operation carries an appreciable mortality (12-15%) and its difficulty lies chiefly in the complete eradication of adrenal tissue. It is estimated that about one-third of the patients have accessory adrenal tissue outside the actual gland itself. There seems considerable basis for the belief that oophorectomy, combined with cortisone therapy, achieves as much as the technically difficult operation of adrenalectomy.

HYPOPHYSECTOMY is, at the moment, the last ditch in the hormonal-surgical attack on advanced mammary carcinoma. Heretofore, it has been difficult to select suitable cases, except on a purely empirical basis, but Hadfield's recent work in estimating urinary prolactin may give a very useful pointer.

At least half the cases submitted to this operation obtain a very definite symptomatic improvement, and this percentage may well be increased when selection is more accurate. The operation, of course, demands the very specialised technique of a skilled neuro-surgeon. It has the advantage that it does not produce the pronounced upsurge of mammatrophic activity that adrenalectomy does. In fact, the post-operative management of a case of hypophysectomy is much easier if

the adrenals are still intact. Adrenalectomy preceding hypophysectomy tends to produce a very marked instability of fluid and electrolytic balance.

The side-effects of hypophysectomy must be borne in mind. Approximately half the cases will get subsequent diabetes insipidus and all will show greatly decreased thyroid function. Such a state of affairs calls for permanent post-operative treatment in either or both of these directions.

Conclusions

From all this mass of facts and theories, can one extract a practical *modus operandi*? I like this series of simple questions which Moore and Jessiman suggest should be asked in assessing each particular case:

1. At what stage in the natural course of the disease is the patient when first seen?
2. What has surgery, radical or local, to offer?
3. Has irradiation therapy a place?
4. Is the tumour hormone-dependent?
5. If so, what is the probable source of the hormone?
6. Can its removal by hormonal therapy or endocrine operations help the case?

These may be simple questions to ask; they are still not so easy to answer. But a great deal can be learnt about the activity of any growth by a careful study of symptoms and signs including discoverable visceral and soft tissue metastases and the radiological findings, and by the application of the tests previously described.

One feels, however, that a complete reorientation of thought on the problem is urgently needed. The first essential in any case is the discovery of the hormone dependence of the growth. We should aim to achieve this *before* and not after the appearance of metastases. If this were possible, then the unfortunately larger group of non-dependent growths would be treated by a judicious mixture of surgery and deep X-ray therapy. To consolidate my own ideas, I believe that in this group, radical mastectomy alone is the treatment of choice for genuine clinical Stage I growths in the outer quadrants; that Stage I growths in the inner quadrants call for radical mastectomy together with irradiation of the internal mammary and supra-clavicular fields of lymphatic spread and that, for all other cases, local and non-mutilating surgery, with carefully planned deep X-ray therapy, is indicated.

In the hormone-dependent class, there would seem every indication for proceeding with a similar basic plan, reinforced without delay by surgical castration and supportive cortisone therapy. In those cases which break down under such a regime, hypophysectomy should be seriously considered.

One realises that such a simplification and condensation of thought is full of fallacies, but it does embody two principles—that of turning a full battery of therapeutic guns, carefully arranged and accurately trained, on to the target of growth and, secondly, that of sparing the patient as much discomfort and disfigurement as possible in the process.

Thus, while sadly *cure of the disease* still eludes us, *care of the patient* can be exercised to the full.