THE HORMONAL MANAGEMENT OF ADVANCED CARCINOMA OF THE BREAST *

PERCY HELMAN, M.B., CH.B. (CAPE TOWN), F.R.C.S. (ENG.)

Department of Surgery, University of Cape Town

Although more than half a century has passed since the first reported effects of endocrinal control of breast cancer, our ignorance of the factors involved remains as profound as ever. The uncertainties and oddities of the natural history of this disease can be matched only by the confusion that exists in efforts to control it.

Periods of acclamation and condemnation of treatment follow each other in rapid succession in this branch of medicine. The problem of management of the advanced or disseminated form of the disease is clouded by an overwhelming feeling of hopelessness and helplessness. Should there be heroic treatment? Should there be minimal treatment, or should there be no treatment at all? Which hormones are to be given to, and which are to be withdrawn from, these most distressed sufferers?

During the 7 years from 1954 to 1960, 986 female and 10 male patients with breast cancer were seen and treated at Groote Schuur Hospital, Cape Town. Of these, 250 female and 2 male patients received hormone therapy as the main and, in most cases, the only form of treatment during some stage of their disease. This paper is based on a review and follow-up of these 252 patients, in an effort to gain some clarity about the efficacy of treatment.

ENDOCRINAL ASPECTS OF MAMMOGENESIS AND BREAST CANCER

The hormonal treatment of breast cancer is based on the premise that the progressive growth of breast cancer is controlled by the *same* group of hormones that are essential for normal mammogenesis. While many authorities accept this without reservation, results of treatment do not seem to bear this out.

Oestrogens, progesterone and prolactins are responsible for mammary growth, particularly for the early mitotic phase.[1-3] Prolactin can also stimulate the mammary alveoli to secrete milk,[4] and can stimulate cell division in the mamma.[5] The addition of growth hormone[6] and ACTH[3] can induce lactogenesis. Gonadotrophins are also important, because they have been shown to induce mammary hyperplasia when combined with oestrogens.[7]

Other hormones acting on the breast are oxytocin from the posterior pituitary and thyroxin, which play their part in milk expulsion into the ducts and in the maintenance of the optimum yield of milk.[8,9] Recently a complex pattern of pituitary control by the hypothalamus has been demonstrated and this, too, may indirectly influence breast development.[10,11]

THE PROBLEM OF THE ENDOCRINAL CONTROL OF BREAST CANCER

1. Hormone therapy modifies the growth of human breast cancer in less than 50% of patients, and fails to relieve the majority of patients.

2. Hormonal control, when it does occur, is always of a temporary nature and never seems to cure any patient with breast cancer.

3. A small number of patients may actually have the disease aggravated by what would appear to be adequate hormone therapy — a hazard which undoubtedly shortens life.

4. Spontaneous regression of breast cancer is very well known and is often related to naturally occurring hormonal environmental changes — for example, during pregnancy,[12] lactation[13] or the menopause[14-16] — and rarely may be mistaken for therapeutic response.[17] Occasionally, however, the progress of the disease cannot be explained on a basis of hormonal alteration.[18]

Furthermore, there are no adequate means of assessing the endocrine status of any one patient in order to predict the response to any hormone manoeuvre. In other words, there is no scientific basis for any particular form of treatment. Lowered oestrogen excretion in any one patient need not be accompanied by an objective remission of the disease. It may, in fact, be associated with aggravation of the disease. Oestrogen excretion in patients with remission and those with progressive disease after oophorectomy or even after bilateral total adrenalectomy may be quite indistinguishable. Not even after adrenalectomy or hypophysectomy can one rely on the level of urinary oestrogen to predict a response.[19-23] So much for oestrogen dependence.

Resurgence of oestrogenic activity may occur with progression of the disease even after complete hypophysectomy.[24] It has also been shown that relapse after adrenalectomy is not associated with the development of functioning adrenocortical or accessory adrenocortical tissue. It is justifiable to assume that the temporary nature of the response, after adrenalectomy at any rate, results from the ability of cancer cells to resume active growth in the absence of hormonal factors.[25]

Recently, claims have been made that the ratio of 11-deoxy- to 11-oxy-17-ketosteroids correlates with the patients' response.[26] Others have claimed that the urinary assays of 17-hydroxycorticosteroids and aetiocholanolone may be of value in selecting patients for endocrinal ablative surgery.[27]

There is also conflicting evidence about the mechanism of the 'anti-tumour' activity of these hormones. There is no evidence to suggest that any one hormone is directly anti-tumour in its action. The fact that oestrogens may inhibit in the postmenopausal and stimulate in the premenopausal patient adds weight to the idea that no hormone is directly anti-tumour in its action.[28] It has already been shown that treatment is not a simple matter of reduction of endogenous oestrogen. All the evidence seems to point to a non-specific action on the part of the hormones, i.e. a change which comes about as result of a non-specific alteration of hormonal environment.[7]

GROOTE SCHUUR HOSPITAL POLICY OF HORMONAL TREATMENT

A few years ago it was decided to institute a uniform policy of treatment for patients with advanced breast cancer at Groote Schuur Hospital. In this way a large enough series could rapidly be built up, from which important lessons would be learnt. It was also felt that by this method deficiencies in treatment could rapidly be rectified.

The policy of treatment was planned by representatives from the Departments of Surgery, Radiotherapy, Pathology, Pharmacology and Physiology, under the chairmanship of Prof. J. H. Louw. A very conservative policy was adopted for reasons which I have already enunciated, but which may be summarized as follows:

1. Hormone therapy modifies growth in human breast cancer in less than 50% of cases.

2. Regression with hormone therapy is always of a temporary nature.

3. Hormone therapy may aggravate the disease.

4. There is no way of accurately predicting response to treatment.

* Based on a paper presented at the 43rd South African Medical Congress (M.A.S.A.), Cape Town, 24 - 30 September 1961.

Patients suitable for hormone therapy were considered to be those whose disease had progressed beyond the scope of surgical or radiotherapeutic treatment. Occasionally patients were given hormone therapy combined with radiotherapy or cytotoxic drugs, where the latter methods were considered to be of palliative value only, and not capable of controlling the disease by themselves.

Treatment was indicated when symptoms and signs such as pain, cough, dyspnoea, anaemia, or extending local disease were present. Evidence of progression of the disease was a strong indication for treatment, and so was advanced local disease and inflammatory cancer of the breast. Patients with symptom-free, small skeletal and pulmonary metastases were treated only when these metastases produced symptoms. The presence of massive liver metastases was shown to be a contraindication to hormonal treatment. While emphasis was placed on conservatism, every effort was made to counter any pain or discomfort that the patient might be suffering.

A decision had to be taken on what constituted the division between menopausal and truly postmenopausal status, for the purpose of this treatment. Early on, the division was set at 60 years, but later it was felt that all women under 50 should be regarded as premenopausal and those over 60 years should be placed in the postmenopausal group. Those between 50 and 60 years were classified according to the vaginal oestrogenic index and urinary follicular-stimulating-hormone (FSH) estimation. More recently we have followed the advice of others in setting the dividing line at 5 years past the menopause, whether the menopause was artificially induced or not.

With regard to actual treatment, it was suggested that the simple hormonal manoeuvres be tried first, and then only one at a time, the idea being to have another manoeuvre available should the patient relapse after treatment or not respond at all. Favourable response to simple hormone manoeuvres, such as oophorectomy or androgen therapy, was looked upon as an indication for more drastic hormone treatment, such as adrenalectomy or hypophysectomy, but only when the patient's disease relapsed.

The following is a brief outline of the regime followed on our patients:

A. Premenopausal and Menopausal Patients

Step I. Bilateral oophorectomy.

Step II. Androgen therapy.

Step III. Bilateral total adrenalectomy or hypophysectomy. These operations were performed on patients responding to either step I or step II.

The indications for bilateral total adrenalectomy and for hypophysectomy, as far as advanced breast cancer is concerned, are basically identical. In this series, adrenalectomies were performed on patients from the larger centres, and within easy reach of medical attention. Hypophysectomies were performed on the so-called 'country' patients, in less easy reach of urgent medical attention. This was done simply because the postoperative hormonal control of the hypophysectomized patients was less difficult and usually less urgent than that of the adrenalectomized patients.

Step IV. Cortisone and thyroid-extract administration, for those who showed no response to any hormones, or after relapse following step III.

B. Postmenopausal Patients

Step I. Oestrogen therapy.

Step II. Androgen therapy.

Step III. Hypophysectomy. For those who showed response after step I or step II.

Step IV. Cortisone and thyroid extract (as above).

Regime in Males

For males of all ages with disseminated breast cancer, orchidectomy was advised. This was performed on 2 of our patients, with gratifying results. Pain relief occurred in both and one is alive and well 3 years after the operation.

HORMONAL THERAPY

Bilateral Oophorectomy

The rationale of this form of therapy is the removal of the source of oestrogen and progesterone. Progesterone removal also facilitates the removal of the so-called harmful effects of the gonadotrophins.

Castration is the original method of endocrinal treatment of breast cancer.[29,30] During the early part of this century very many patients with advanced mammary cancer had been castrated.[31-35] After World War II, a further spate of publications appeared in an attempt to evaluate this form of treatment.[36-40] These reports indicated an objective improvement in between 22 and 44% of the patients so treated. Treves[37] showed that the earlier the castration, the higher the response rate, but he also pointed out that in patients with local recurrent disease after mastectomy, the response was significantly improved the

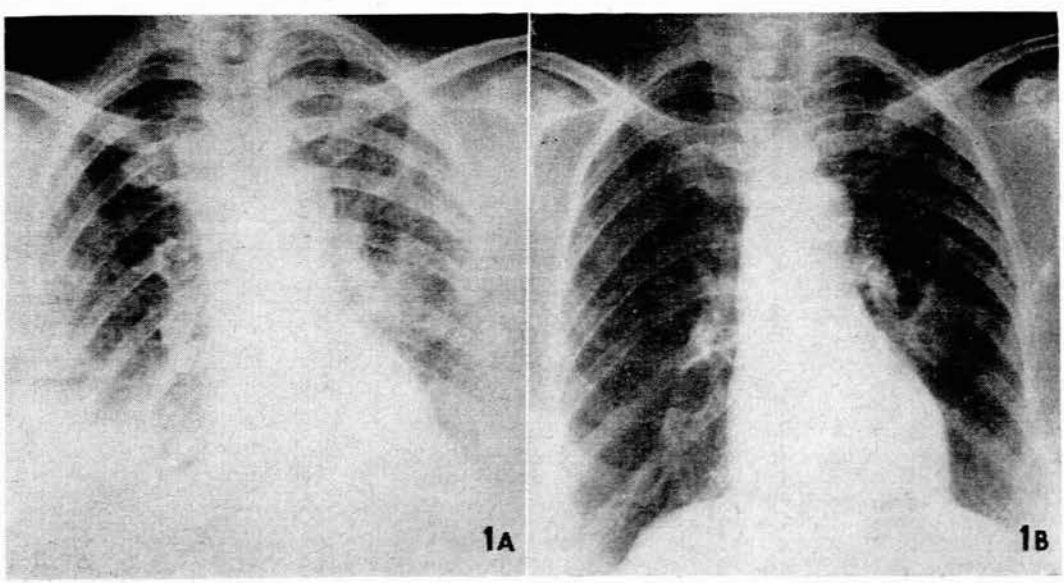

Fig. 1. Patient with secondary lung deposits. *A.* Chest X-ray shortly before oophorectomy. *B.* Chest X-ray 4 months after oophorectomy. Note the vast improvement.

longer the interval between mastectomy and oophorectomy. Why the patients with demonstrable ovarian metastases and those whose ovaries failed to show cortical stromal hyperplasia survived for longer periods,[41] is not at all clear.

In the Groote Schuur Hospital series, 110 bilateral oophorectomies were performed between 1954 and 1960 on patients with breast cancer. In one patient the operation had to be abandoned because of extensive malignant infiltration of the pelvis making mobilization of the ovaries quite impossible.

The indications for oophorectomy are shown in Table I. From this it will be seen that 107 operations were performed for the advanced disease. The response to oophorectomy is shown in Table II.

TABLE I. THE INDICATIONS FOR OOPHORECTOMY

Indication	*No. of patients*
Bone metastases	34
Extensive local disease	32
Intrathoracic disease	30
Termination of pregnancy (with advanced disease)	4
Abdominal metastases	3
Cerebral metastases	2
Neck nodal swellings	2
Prophylactic castration	3
Total	110

In this series, objective response was meant to denote the visible or radiographic improvement of local or distant metastases, though not necessarily all metastases. While improvement occurred, no other metastases were seen to become degenerate or aggravated. The improvement of some and aggravation of other metastases is quite a common finding in breast cancer. This mixed form of response was classified in this series as being a subjective improvement, which was also meant to denote a simple relief of pain, and improvement of appetite, weight and general health.

TABLE II. THE RESPONSE TO OOPHORECTOMY IN 107 PATIENTS

Response	%
Objective response	18·8
Subjective response	10·3
No change	64·4
Worse	6·5

The average age of those patients who responded was 41 years and the length of improvement varied from 2 to 36 months.

The following 2 reports give examples of the remarkable improvement that sometimes follows oophorectomy:

1. E.A., aged 46 years. She presented with stage-4 carcinoma of the right breast in 1960. Secondary deposits were detected in the lung parenchyma and cervical and thoracic spines. Bilateral oophorectomy was performed on 23 March 1961. Four months after this operation the breast lump was much smaller and the lung fields greatly improved. The relevant X-rays are shown in Figs. 1A and B.

2. A.D., aged 38 years. A left radical mastectomy for stage-2 carcinoma was performed on 22 March 1957. By February 1958 widespread metastases became obvious in the spine, pelvis and sacrum. The extensive spinal infiltration resulted in paresis and incontinence of urine, and the patient had to be nursed on a Stryker bed. Soon afterwards an oophorectomy was performed, and later she was given 'durabolin', which she is still having. The improvement that followed was truly remarkable. The X-ray plates of the pelvis, before and after operation, are shown in Figs. 2A and B. The X-ray appearance is virtually normal now, and she is still very fit and pursuing her teaching profession with tremendous vigour.

Ovarian irradiation was performed on 11 of our patients, mainly because 9 were considered to be too ill for oophorectomy, and 2 refused surgical intervention. Two of these patients improved objectively, while the others were mainly unresponsive.

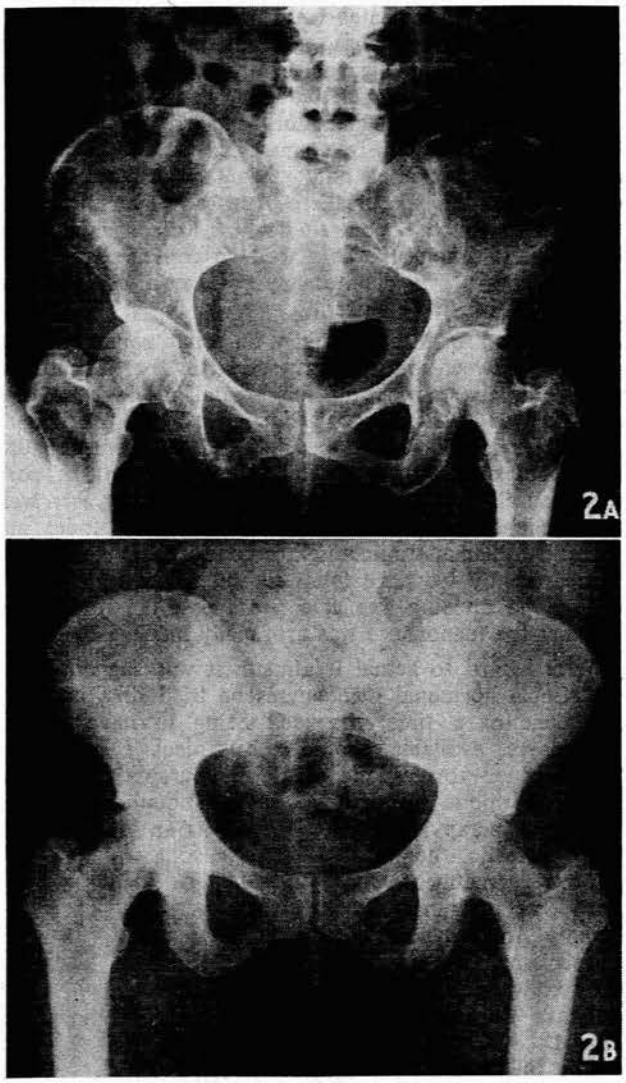

Fig. 2. Patient with widespread bony metastases. *A.* X-ray of pelvis in February 1958, showing extensive osteolytic metastases. *B.* X-ray of pelvis 6 months after oophorectomy showing the remarkable improvement.

The following case history depicts the response that may occur following ovarian irradiation:

G.M., aged 36 years. She was first seen in September 1956 with a stage-3 growth, i.e. a large adherent mass with *peau d'orange*. This was treated by deep X-ray therapy. In February 1958, metastases in the lung parenchyma became obvious, and ovarian irradiation was resorted to. She was also given some

androgen therapy at that time. Five months later there was great improvement in her general condition as well as in her lungs. Figs. 3A and B show the relevant X-rays. It must be stressed that in this patient androgen therapy followed soon after the ovarian irradiation, and the improvement may be due to this treatment as much as to the ovarian ablation. This patient underwent bilateral total adrenalectomy in September 1958, from which she improved as well, but she died from the disease in January 1959.

References in the literature report a response rate of between 33 and 70% for patients undergoing ovarian irradiation.[42-45] The duration of therapy is apparently the important consideration, and the ovaries of young women are said to be more resistant to therapy than those of women in the late phase of menstrual life.[46]

Androgen Therapy

The rationale of this form of therapy is said to be its antagonistic action towards oestrogen and its inhibiting effect on the gonadotrophins, which result in diminished output of oestrogen and progesterone from the ovary. The effect is said to be the same as bilateral total oophorectomy.

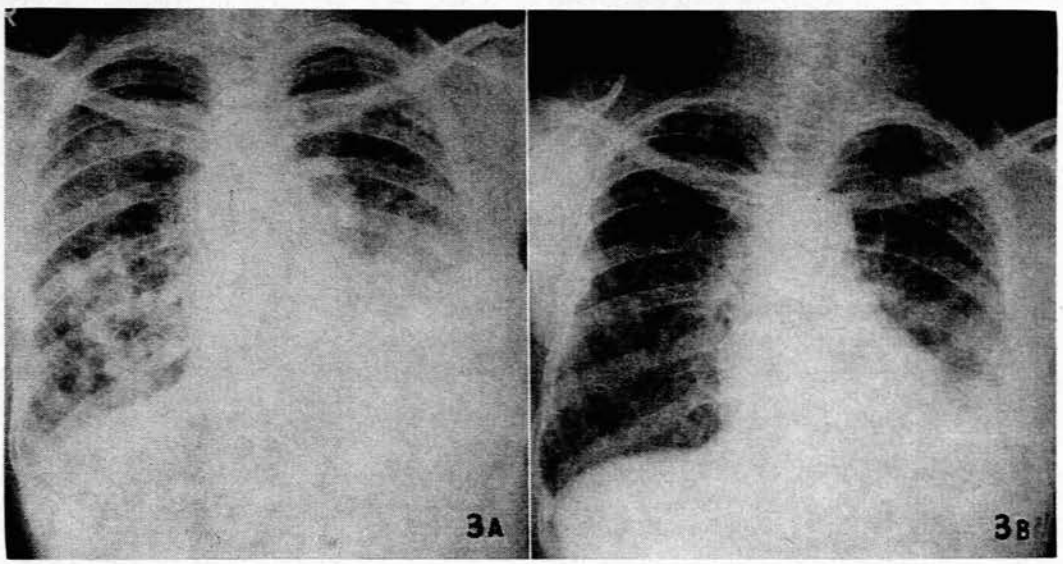

Fig. 3. Patient with extensive lung secondary deposits. *A*. Chest X-ray in February 1958, shortly before ovarian irradiation. *B*. Chest X-ray in November 1958. Note marked improvement in appearance of the lungs.

Reports of series of androgen therapy are not lacking.[14,47-51] In the present series, effective androgen therapy (longer than 3 weeks) was administered to 139 patients. The androgens employed are shown in Table III.

TABLE III. THE VARIOUS ANDROGENS USED

Androgens	*No. of patients*
Testosterone phenylpropionate (TPP)	79
Halotestin (fluoxymesterone)	22
Durabolin (nor-androstenolone phenylpropionate)	14
Testosterone implant	14
Others	10
Total	139

Androgen therapy followed oophorectomy in 73 patients, irradiation castration in 8, and oestrogen therapy in 17. The remaining 41 patients were given androgens as the first step of the hormone therapy. Table IV shows the response to androgen therapy.

TABLE IV. THE RESPONSE TO ANDROGEN THERAPY

Response	%
Objective response	7·2
Subjective response	15·9
No change	74·8
Worse	2·1

The advent of generalized body pains soon after androgen administration was a sure sign that the hormone was aggravating the disease. 'Halotestin' (fluoxymesterone) produced a feeling of immense well-being and, since it can be given orally, was found to be a most suitable drug. The reported enlargement of the clitoris was not observed. It is said to be 7½ - 15 times as active, weight for weight, as sublingual methyltestosterone, and shows relatively less virilism than some of the other known androgens.[52-54]

All androgens are still liable to produce serious hypercalcaemia, resulting in far-reaching renal damage and serious deterioration of the metastases. The anti-tumour activity of the androgens used did not seem to vary with the different types. We were equally satisfied and disappointed with all of them.

In an interesting series, 17 patients, whose average age was 62 years, were given androgens after a course of oestrogens. It was found that when the oestrogens improved the condition, the androgens generally did so too, and when the one hormone failed to elicit a response, the other also failed. In 2 patients, however, the androgens used did seem to produce some objective improvement, even though the oestrogens had failed to do so.

The following case history is an example of the degree of response that may be obtained with androgens:

S.P., aged 54 years, was first seen in February 1956 with a fixed and ulcerating growth of the breast of 8 years' duration (Fig. 4A). She was also coughing and breathless because of a pleural effusion, presumably caused by pleural metastases. The local lesion was treated by deep X-ray therapy, and because of the presence of secondaries, androgens (TPP and later durabolin) were also prescribed. She improved rapidly, and Fig. 4B shows the remarkably healed local lesion 2 years later. The chest disease also improved, and stayed controlled and unchanged for 5 years with continuous androgen therapy. By April 1961 she again became breathless, and soon afterwards died from extensive lung metastases. This case illustrates the controlling effect that may occur with androgens.

The inclusion of androgens as one of the forms of treatment does improve the lot of a few patients with breast cancer, and I feel that it should not be discarded, as has been suggested by some.[55]

Oestrogen Therapy

This form of therapy is irrational and difficult to explain. It is said to inhibit the pituitary FSH, particularly when the ovaries are inactive, as in truly postmenopausal women.[7,56] Theoretically, therefore, oestrogens may be given to premenopausal patients, but only after castration. I know of no such series, however. Oestrogens are also said to encourage hyperplasia and sclerosis of elastic tissue and thus to improve the repair around the tumour.[57] The use of oestrogens in the treatment of advanced breast cancer is well reported in the literature.[16,58-60]

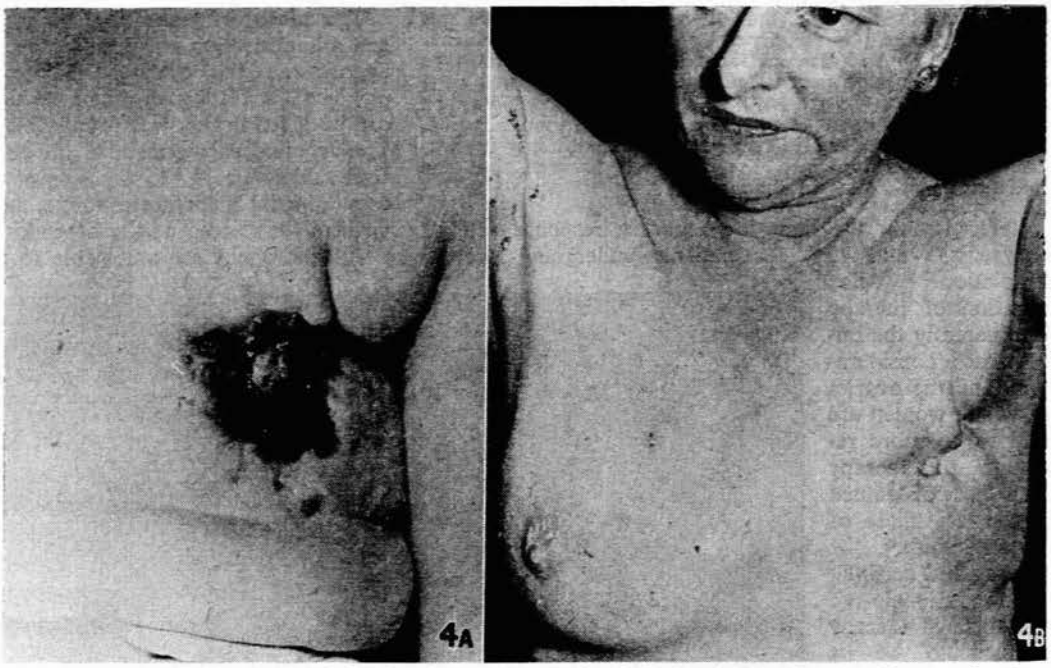

Fig. 4. Patient with advanced, fixed, ulcerating growth of the breast. *A*. Showing the growth. An underlying pleural effusion was also present. *B*. Two years after a course of deep X-ray and persistent androgen (TPP and durabolin) therapy. This picture shows the degree of healing that took place.

TABLE V. THE INDICATIONS FOR OESTROGEN THERAPY

Indication	*No. of patients*
Advanced local disease	29
Intrathoracic disease	25
Bone metastases	23
Abdominal metastases	8
Cerebral metastases	1
Supraclavicular nodal swelling	1
Soft-tissue metastases	1
Total	88

In the present series, 88 patients were treated with oestrogens, using mainly hexoestrol and stilboestrol in the highest tolerable doses. The indications for oestrogen therapy are shown in Table V, and the response to oestrogen therapy in Table VI.

Limiting factors in the use of oestrogens were the relatively high incidence of nausea with big doses, and occasional uterine bleeding, resulting in drastic reduction of dosage or temporary cessation of therapy.

A very full review of androgen and oestrogen therapy has recently been published,[15] and the frequency of tumour regression was 21·4% in the androgen-treated group and 36·8% in the oestrogen-treated group. Our figures do not reach these impressive levels.

TABLE VI. THE RESPONSE TO OESTROGEN THERAPY

Response	%
Objective response	11·4
Subjective response	9·2
No change	79·4
Worse	0·0

The following case history shows the remarkable effect of deep X-ray therapy combined with oestrogen therapy:

J.K., aged 76 years. She was first seen in November 1956 with an extensive ulcerating growth of the breast (Fig. 5A). Deep X-ray therapy was applied to the local lesion, but because the radiotherapist felt that the disease was too extensive for effective and radical radiotherapy, oestrogen therapy was added. The lesion rapidly improved, and now, 5 years later, the lesion is still healed (Fig. 5B). Unfortunately a biopsy was not taken and the diagnosis of cancer has not been proved, though clinically it was never in doubt.

Bilateral Total Adrenalectomy

The rationale of this form of therapy is the removal of a remaining source of oestrogen, preferably after oophorectomy. Preliminary removal of the ovaries is desirable and indeed helpful in deciding whether adrenalectomy will be of value. It is seriously questioned whether the good results of adrenalectomy are not mainly due to the added effect of oophorectomy, since the adrenals are only a small source of oestrogen, and the reported effects are not nearly as good as when the ovaries are not removed. An extensive literature has developed on bilateral total adrenalectomy.[61-69]

Fracchia[70] presented a series of 758 patients who had undergone bilateral total adrenalectomy with a mortality rate of 8%, an objective response rate of 43·6%, and a failure rate of 48%. Remissions were generally less than a year, only 25% survived for longer than 1 year, and only 6% for longer than 2 years.

In the present series, 24 patients were subjected to this

operation. Almost all the first 6 patients died very soon after the operation, mainly because their disease was so advanced. Of the remaining 18 patients, 4 improved objectively, 6 subjectively, and 7 not at all. One was made worse, in spite of the fact that she did improve after oophorectomy. The average survival was 12·3 months and all but 1 are now dead.

Hypophysectomy

The rationale for this operation is the removal of gonadotrophin, prolactin, growth hormone and ACTH. In this manner all hormones responsible for mammogenesis are eradicated. As with other forms of hormone therapy, an enormous literature has developed on this subject,[71-74] as well as around the problem of radiotherapeutic destruction of the hypophysis.[75-77]

Pearson and Ray,[74] who recently published their experiences and results with 343 patients undergoing surgical hypophysectomy, found a mortality rate of 6%, and an objective remission rate of 42%, with the duration of remission lasting 11 - 12 months.

Because of careful selection, we have had occasion to refer only 7 patients to our neurosurgical colleagues for hypophysectomy. Only 1 patient responded objectively. This 65-year-old nulliparous patient, with a very advanced local growth of 4 years' duration, and skeletal and pulmonary metastases, showed some response to androgens. After hypophysectomy her general condition improved greatly; this improvement was associated with sclerosis of her bony deposits. She died with relapse of the disease 1 year after the hypophysectomy.

Because of careful selection and insistence that an indication for extensive ablative procedures (adrenalectomy and hypophysectomy) only arises after definite response to lesser hormonal manoeuvres, our figures for these procedures have been kept within modest limits. At Groote Schuur Hospital we have refrained from doing indiscriminate and extensive hormone operations, because it has been felt that the wisdom of performing these operations as a first measure in the treatment of advanced breast cancer has still to be proved.[78]

Smithers[79] has criticized hypophysectomy and has shown that 75% of those treated have had no worth-while improvement, and this has to be set against the added troubles of painful treatment and serious disabilities. There also seems to be a difference of opinion about which ablative procedure is preferable. Not everyone can agree with Atkins that hypophysectomy is to be preferred to adrenalectomy.[80,81] Further reports on these problems are eagerly awaited.

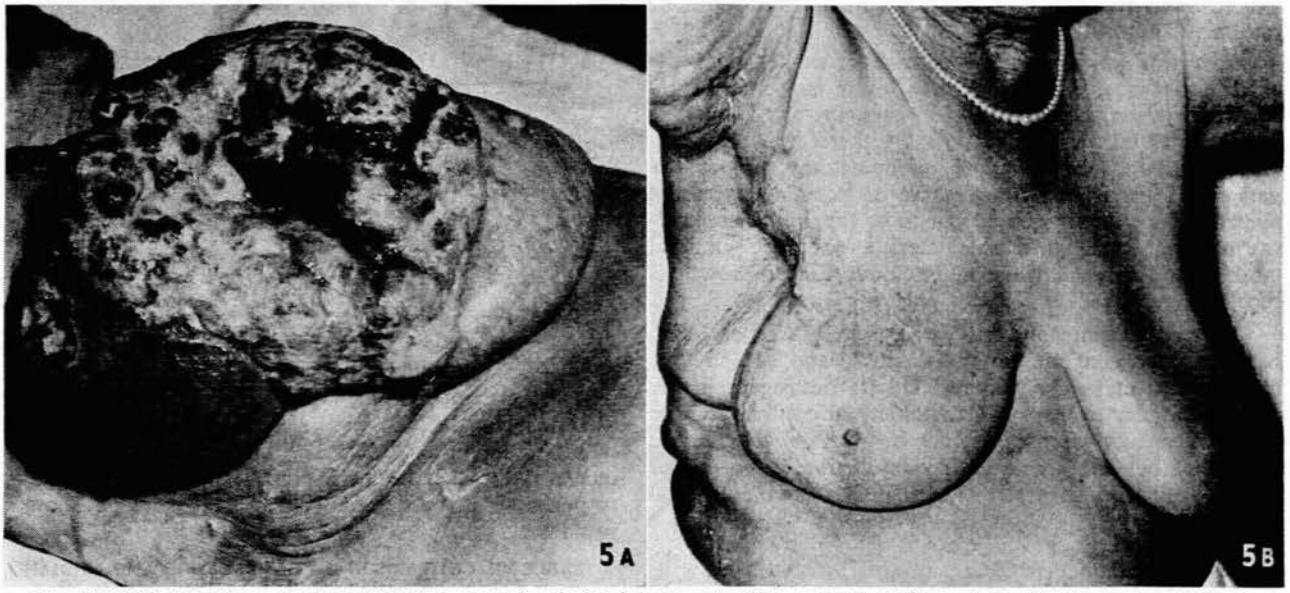

Fig. 5. Patient with extensive ulcerating growth of the breast. *A.* The growth before deep X-ray and oestrogen therapy. *B.* The remarkably healed breast lesion 5 years later.

Cortisone Therapy

During the years 1954 - 1960, cortisone together with a thyroid extract was given to 16 of the patients in this series. In this way a 'medical hypophysectomy' was attained.[82] All these patients were extremely ill and had not responded to any of the previous hormone manoeuvres, or were too ill for either adrenalectomy or hypophysectomy. The average survival of these patients was 9·4 months, and no patient showed objective improvement, although 4 were improved subjectively.

One patient, *B.P., aged 44 years,* is an exception. Six months after a radical mastectomy and deep X-ray therapy for a stage-2 growth, she developed intracranial secondaries, which resulted in blindness, headaches and later coma. She responded dramatically to oophorectomy and walked out of hospital feeling very well. She was readmitted 6 months later with a relapse, and in coma. She was considered too ill for adrenalectomy, but was given cortisone instead, almost as a desperate measure. Again she responded dramatically and regained full consciousness, but was left with a severe visual defect. The improvement has lasted 2 months to date. This one case has taught us that dramatic improvement may follow steroid therapy in patients who are hormone-responsive, and bears out Daniel's contention[55] that steroids are valuable provided ovarian function has ceased.

Lemon[83] has stated that the mean duration of remissions and the percentage of objective remissions can be quite significant with adrenal corticoid therapy only, and can even compare favourably with the remissions in those patients treated by bilateral adrenalectomy, or by hypophysectomy. The usefulness of bilateral oophorectomy and prednisone therapy in advanced breast lesions has been stressed by Brinkley and Pillers.[84]

Age Groups and Response to Hormone Therapy

The incidence of response was investigated in various age groups, irrespective of the diverse methods of hormone treatments applied (Fig. 6).

There was an increased incidence of response at the extremes of age, and a distinctly lower incidence of response between the ages 51 - 60 years, i.e. the immediate postmenopausal years. Theoretically, therefore, the young patient responds best, say, to oophorectomy, but as she gets older, she approaches a phase of lessening hormonal control. The critical years appear to be the immediate postmenopausal years when she enters a phase of minimal control, and in fact, when autonomous cancer growth is most likely.

The truly postmenopausal patient, on the other hand, becomes increasingly hormone-sensitive, and as she ages is more and more likely to respond (to oestrogens in her case). This may explain why the older patient lives longer; this longer survival may simply be part of the natural history of her cancer, or it may be an indication of her greater response to treatment than her premenopausal sister.

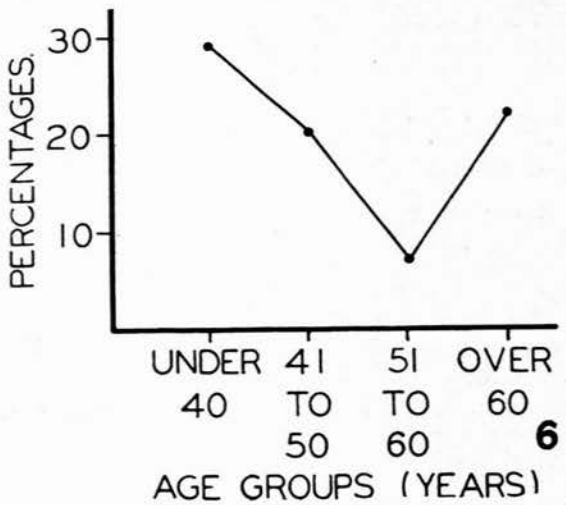

Fig. 6. Incidence of response to hormonal treatment in various age groups.

SURVIVAL RATES

These have been studied in 198 females who have died following hormone therapy. The 52 females still alive in this series have been excluded for statistical reasons.

Fig. 7 shows the survival period in the unselected series. The main facts it brings out are that it is rare for patients to survive beyond 30 months, and that 50% of the patients are dead within 9 months.

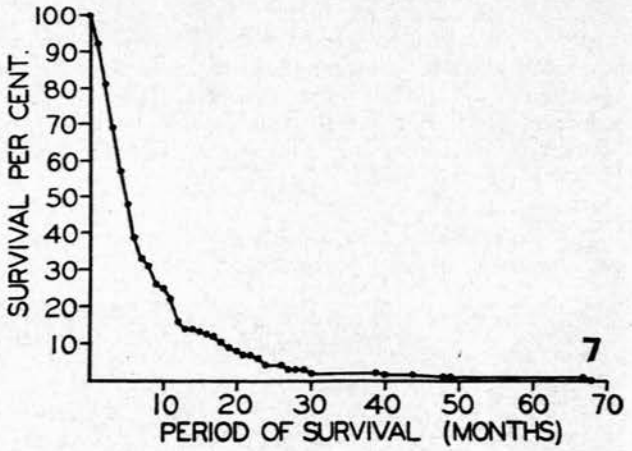

Fig. 7. Percentage of unselected patients surviving specified periods.

Table VII compares the survival rates of the younger with the older patients, and further subdivides the patients into those who do and those who do not respond to hormone therapy.

The figures show that those patients who responded to hormone manoeuvres, irrespective of whether they were pre- or postmenopausal, survived about 4 times as long as those who did not respond, i.e. 21·8 months compared with 5·4 months. Statistically it is clear that treatment increases the survival period of those patients who show response to it, in comparison with those who show no response.

TABLE VII. COMPARISON OF THE AVERAGE AND MEDIAN SURVIVAL PERIODS OF PATIENTS RESPONDING TO TREATMENT WITH THOSE OF PATIENTS NOT RESPONDING

	Responding to treatment			*Not responding to treatment*		
Patients	*No. of patients*	*Average period of survival (months)*	*Median period of survival* (months)*	*No. of patients*	*Average period of survival (months)*	*Median period of survival* (months)*
Premenopausal and menopausal	22	19·45	17·00	106	5·36	3·89
Postmenopausal	12	26·00	21·00	58	5·43	3·66
All patients	34	21·76	—	164	5·38	—

* The median period of survival is the length of time that half the group survives.

The difference in mean survival periods for menopausal and postmenopausal patients who respond to the treatment is highly significant (using Student's 't' test). This suggests that treatment may be more effective for postmenopausal than for premenopausal patients, or simply that postmenopausal patients live longer with their disease.

There is no significant difference between the mean survival periods of pre- and postmenopausal patients who do not respond to treatment. It would also appear that the survival period of those patients with advanced disease who do not receive hormones, is similar to those who do not respond, namely 5 - 6 months.

CONCLUSIONS

The results of this series show that altogether 48 patients, 34 dead and 14 still surviving, were improved by hormone

therapy, i.e. 21% of our patients, and that they survived up to periods of between 20 and 30 months. These figures only emphasize the dreadful and relentless course of breast cancer.

Critics may argue that if these figures reflect the results of treatment of the advanced disease, a good case could be made for much earlier hormone therapy and some may even suggest prophylactic endocrinal treatment. This proposal may be strengthened by a more detailed analysis of all our patients, which shows that a further 201 patients have died without the benefits of hormone treatment. Economic and social difficulties, preventing patients from attending the breast clinic at Groote Schuur Hospital, have been mainly responsible. Only determined follow-up of these patients has shown that they died without returning to the hospital after the initial surgical or radiotherapeutic treatment. Very early administration of hormones to these patients living so far away may possibly have resulted in an improved prognosis.

At the same time it must be pointed out that reports of early oophorectomy and adrenalectomy[85] or prophylactic castration do not convincingly show longer survival.[86,87] The figures of these series show a tendency towards longer survival, but the statistical significance of the results may be questionable, because in some cases the castration was performed long before the onset of the cancer, while in others it was performed at the time of the mastectomy. In some, androgens were given in addition, while in others the castrated patients represented only a small percentage of the total number for comparison. There is, nevertheless, a tendency towards improved results. A proper survey would be of immense benefit.

In our clinic room we have watched these wonderful people with their awful disease, obviously suffering intense physical and mental agony, and yet appearing so uncomplaining. We have never ceased to marvel at their fortitude and courage. The inadequacy of the treatment is surely an indictment of the whole medical profession. How long must this frustration last?

Sir Norman Moore (1847 - 1922) was quite right when he wrote:

> 'In criticizing the ignorance of the Dark Ages or the Middle Ages, modern writers often forget how very ignorant we ourselves are, or how recent is our knowledge.'

SUMMARY

The policy adopted at Groote Schuur Hospital for the treatment of patients with advanced breast cancer by hormonal means, and the follow-up on 252 patients so treated are presented. The essence of the treatment was its conservatism, and simple hormonal methods were always adopted before severe ablative procedures were resorted to. The results obtained with oophorectomy, androgen therapy and oestrogen therapy are discussed, and the results achieved with adrenalectomy, hypophysectomy and steroid therapy are mentioned.

It was shown that in the immediate postmenopausal period, the response to treatment was less satisfactory than in the much younger or older patient.

Patients responding to treatment survived for significantly longer periods than those who did not respond. It appeared as if the survival period of the non-responding group was equal to that of those patients with advanced disease who did not receive hormone therapy. Postmenopausal patients survived for longer periods than premenopausal patients.

Only 21% of the patients treated showed significant improvement.

A good case can be made for early hormone therapy in patients who, because of economic and social difficulties, coupled with problems of long distances, find it difficult or impossible to attend for breast-cancer follow-up examinations.

My thanks are due to Prof. J. H. Louw for his criticisms, suggestions and encouragement; to Prof. J. Muir Grieve for allowing me the facilities of the Department of Radiotherapy with its careful follow-up system; to Prof. F. D. du T. van Zyl, of the University of Stellenbosch, and Dr. R. L. Kotze, Superintendent of the Karl Bremer Hospital, for allowing me to scrutinize the case histories of all patients referred from the Karl Bremer Hospital to the Department of Radiotherapy, Groote Schuur Hospital; and to Dr. J. G. Burger, Superintendent of the Groote Schuur Hospital, for permission to publish.

My thanks for assistance also go to Drs. M. B. Bennett, W. Wilkie, W. Silber, R. Sealy, and J. Anderson, the other members of the Breast Clinic; Mr. J. Hampton, Department of Commerce, UCT, for statistical help; Mrs. R. Kottler for the illustrations; Mr. G. McManus and Mr. B. Todt for the photographs; and Messrs. Upjohn for generous supplies of halotestin.

REFERENCES

1. Hadfield, G. (1958): Ann. Roy. Coll. Surg. Engl., **22**, 73.
2. Nelson, W. O (1952): Ciba Colloq. Endocr., **4**, 402.
3. Lyons, W. R. *et al.* (1955): In *Hypophyseal Growth Hormone. International Symposium*, p. 461. New York: McGraw-Hill.
4. Bradley, T. R. and Clarke, P. (1956): J. Endocr., **14**, 28.
5. (*a*) Mizuno, H. *et al.* (1955): Endocr. jap., **2**, 163.
   (*b*) *Idem* (1956): *Ibid.*, **3**, 227.
   [Quoted by Cowie, A. T. and Folley, S. J. *in* Currie, A. R. ed. (1957): *Op. cit.*[35], p. 266.]
6. Riddle, O. *et al.* (1933): Amer. J. Physiol., **105**, 191.
7. Lazarev, N. I. *in* Raven, R. W. ed. (1960): *Cancer Progress*, p. 204, London: Butterworth.
8. Benson, G. and Folley, S. J. (1957): J. Endocr., **16**, 189.
9. Welbourn, R. B. *in* Carling, R. E. and Ross, J. P. eds. (1959): *Surgical Progress (British Surgical Practice)*, p. 247. London: Butterworth.
10. Harris, G. W. (1955): *Neural Control of the Pituitary Gland*. London: Arnold.
11. Leading article (1956): Brit. Med. J., **1**, 970.
12. Foulds, L. (1949): Brit. J. Cancer, **3**, 240 and 345.
13. White, T. (1954): Ann. Surg., **139**, 9.
14. Hadfield, G. and Holt, J. (1956): Brit. Med. J., **2**, 972.
15. Clemmensen, J. (1951): Nat. Cancer Inst. Monogr., **6**, 187.
16. Committee of Research of American Medical Association (1960): J. Amer. Med. Assoc., **172**, 1271.
17. Smithers, D. (1952): J. Fac. Radiol. (Lond.), **4**, 89.
18. Gordon-Taylor, G. (1959): Brit. Med. J., **1**, 455.
19. Bulbrook, R. D. and Greenwood, F. C. (1958): *Ibid.*, **2**, 7, 12 and 15.
20. Swyer, G. I. M. *et al.* (1961): *Ibid.*, **1**, 617.
21. Strong, J. A. *et al.* (1956): Lancet, **2**, 955.
22. McAllister, R. A. *et al.* (1960): *Ibid.*, 1, 1102.
23. Scowen, E. F. *in* Currie, A. R. ed. (1957): *Endocrine Aspects of Breast Cancer*, p. 208. Edinburgh: Livingstone.
24. Jessiman, A. (1959): Ann. Roy. Coll. Surg. Engl., **24**, 213.
25. Sim, A. W. *et al.* (1961): Lancet, **2**, 73.
26. Allen, B. J. *et al.* (1957): *Ibid.*, **1**, 496.
27. Bulbrook, R. D. *et al.* (1960): *Ibid.*, **1**, 1154.
28. Herman, J. *et al.* (1947): Arch. Surg., **54**, 1.
29. Schinzinger, A. (1889): Verh. dtsch. Ges. Chir., **18**, 28. (Op. cit.[*], p. 207.)
30. Beatson, G. (1896): Lancet, **2**, 104.
31. Boyd, I. (1900): Brit. Med. J., **2**, 1161.
32. Herman, G. E. (1900): *Ibid.*, **2**, 1167.
33. Torek, F. (1914): Ann. Surg., **60**, 476.
34. Thompson, A (1921): Brit. Med. J., **2**, 1538.
35. Lett, H. (1905): Lancet, **1**, 227.
36. Adair, F. *et al.* (1945): J. Amer. Med. Assoc., **128**, 161.
37. Treves, N. (1954): Amer. Practit., **5**, 518.
38. Raven, R. W. (1950): Brit. Med. J., **1**, 1343.
39. Treves, N. and Finkbeiner, J. (1958): Cancer, **11**, 421.
40. Gordon, D. and Segaloff, A. *in* Segaloff, A. ed. (1958): *Second Biennial Louisiana Cancer Conference*, p. 188. St. Louis: C. V. Mosby Co.
41. Osborne, M. P. and Pitts, R. M. (1961): Cancer, **14**, 1.
42. Taylor, G. W. (1939): Surg. Gynec. Obstet., **68**, 452.

43. Dresser, R. (1936): Amer. J. Roentgenol., **35,** 384.
44. Ahlbom, H. (1930): Acta radiol. (Stockh.), **11,** 614.
45. Halberstaedter, L. and Hochman, A. (1946): J. Amer. Med. Assoc., **131,** 810.
46. Nathanson, I. T. and Kelly, R. M. (1952): New Engl. J. Med., **246,** 180.
47. Loeser, A. (1938): Brit. Med. J., **2,** 319.
48. Galton, D. (1950): Brit. J. Cancer, **4,** 20.
49. Segaloff, A. (1959): Cancer, **12,** 735 and 1270.
50. *Idem* (1960): *Ibid.*, **13,** 1017.
51. *Idem* (1961): *Ibid.*, **14,** 195.
52. Brennan, M. J. *et al.* (1960): *Ibid.*, **13,** 1195.
53. Buckle, R. M. (1959): Brit. Med. J., **1,** 1378.
54. Segaloff, A. (1958): Cancer, **11,** 1187.
55. Daniel, O. (1961): Proc. Roy. Soc. Med., **54,** 555.
56. Kennedy, B. J. *et al.* (1957): Cancer, **10,** 813.
57. Emerson, W. J. *et al.* (1953): *Ibid.*, **6,** 641.
58. Haddow, A. *et al.* (1944): Brit. Med. J., **2,** 393.
59. Huseby, R. *in* Segaloff, A. ed. (1958): *Op. cit.*[43], p. 206.
60. Adair, F. E. *et al.* (1949): J. Amer. Med. Assoc., **140,** 1193.
61. Huggins, C. and Bergenstal, D. M. (1952): Cancer Res., **12,** 134.
62. Huggins, C. and Dao, T. (1954): Ann. Surg., **140,** 497.
63. Greening, W. P. and Harmer, M. (1954): Postgrad. Med. J., **30,** 566.
64. Cade, S. (1955): Brit. Med. J., **1,** 1.
65. Helman, P. (1955): S. Afr. Med. J., **29,** 1025.
66. Taylor, S. G. (1956): Amer. J. Med., **21,** 688.
67. Lipsett, M. B. *et al.* (1957): Cancer, **10,** 111.
68. Hellstrom, J. and Frankinson, C. *in* Currie, A. R. ed. (1957): *Op. cit.*[23], p. 11.
69. Pyrah, L. N. *in* Currie, A. R. ed. (1957): *Op. cit.*[23], p. 22.
70. Fracchia, A. *et al.* (1959): Cancer, **12,** 58.
71. Luft, R. *et al.* (1956): Amer. J. Med., **21,** 728.
72. Kennedy, B. J. *et al.* (1956): New Engl. J. Med., **255,** 1165.
73. Barron, D. *et al.* (1958): Brit. J. Surg., **45,** 593.
74. Pearson, O. H. and Ray, B. S. (1960): Amer. J. Surg., **99,** 544.
75. Buxton, P. *et al. in* Currie, A. R. ed. (1957): *Op. cit.*[23], p. 58.
76. Forrest, A. P. M. (1958): Lancet, **2,** 192.
77. Lawrence, J. M. and Tobias, C. A. (1956): Cancer Res., **16,** 185.
78. Raven, R. W. (1961): Brit. Med. J., **1,** 610.
79. Smithers, D. (1960): *Clinical Prospect of the Cancer Problem.* Edinburgh: Livingstone.
80. Joint Committee on Endocrine Ablative Procedures (1961): J. Amer. Med. Assoc., **175,** 787.
81. Atkins, H. B. *et al.* (1960): Lancet, **1,** 1148.
82. Lemon, H. (1951): Proc. Amer. Assoc. Cancer Res., **2,** 225.
83. *Idem* (1959): Cancer, **12,** 93.
84. Brinkley, D. M. and Pillers, E. K. (1960): Lancet, **1,** 123.
85. Patey, D. (1960): Brit. J. Cancer, **14,** 457.
86. Treves, N. (1957): Cancer, **10,** 393.
87. Smith, G. V. and Smith, O. W. (1953): Surg. Gynec. Obstet., **97,** 508.