CORTICOSTEROIDS IN THERAPY OF ADVANCED MAMMARY CANCER

BY

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It is remarkable that in spite of a rather frightening list of side-effects, therapy with corticosteroids is being advocated in a widening variety of diseases. In recent years the use of corticoids in advanced mammary cancer has been reported, and the term "medical adrenalectomy" is becoming increasingly fashionable. While the role of adrenalectomy, as against hypophysectomy, in this disease is still being hotly debated, the role of corticosteroid therapy has not been clarified. The papers published to date on this subject are on small series, and do not agree on such vital points as the proportion of cases responding, the most effective compounds, the optimal dose level, and the relationship between benefit from corticosteroids and that from sex-hormone manipulation or adrenalectomy. Of critical importance also, but so far unestablished, is the selection of cases likely to respond to such therapy, and the possible additive effect of other agents given concurrently.

Since cortisone administration leads to atrophy of the adrenal cortex, its use in cancer of the breast has been loosely referred to as a "medical adrenalectomy," and varying degrees of benefit have been claimed in a number of reports (West *et al.*, 1954; Pearson *et al.*, 1955; Lemon and Reynolds, 1956; Read, 1957; Kolodziejska, 1959). At one extreme it has been suggested that cortisone is as effective as either adrenalectomy plus oophorectomy, or hypophysectomy, both in survival and objective remission rate (Lemon, 1961). At the other extreme it has been graphically stated that "corticosteroids merely allow the breast-cancer patient to walk to the necropsy room" (G. Escher, personal communication, 1960).

In recent years several trials of prednisolone in breast cancer have been reported (Kennedy, 1957; Kofman *et al.*, 1957; Lemon, 1959; Gardner *et al.*, 1962). I have previously reported trials of prednisolone combined with "nitromin" (nitrogen mustard oxide) (Stoll, 1960a), and also of dexamethasone (9 α -fluoro-16 α -methyl-prednisolone) administration in breast cancer (Stoll, 1960b).

Clinical Material and Criteria

This report reviews a total of 154 cases of advanced breast cancer treated by corticoids from 1955 to 1960. This is by far the largest series recorded in the literature. Of this total, 80 were treated by prednisolone alone, a further 49 by prednisolone combined with nitramin, and 25 by dexamethasone. The majority of the two latter series were included in previous reports (Stoll, 1960a, 1960b), but the 80 prednisolone-treated cases are reported for the first time.

Nathanson's classical specification of objective remission from hormone therapy is adopted—namely, a measurable decrease in size of specified lesions, while, at the very least, all other lesions are static and no new lesions appear. The criteria for objective response in specific areas were:

1. *Osseous*.—Recalcification in parts not previously treated by radiotherapy. Fall in serum calcium was *not* accepted as a criterion of response.

2. *Local*.—Decrease in size of breast tumour or ulceration, nodules, or regional nodes, measurable by a ruler and confirmed where demonstrable by photograph. "Arrested" disease is *not* included.

3. *Intrathoracic*.—Decrease in size of radiological opacities in the lungs or of mediastinal nodes, or decrease in the size of a pleural or peritoneal effusion without paracentesis. Gross decrease in the rate of reaccumulation of a serous effusion was recorded but *not* counted as objective control of disease.

4. *Visceral*.—Decrease in size of metastatic hepatic enlargement or decrease in physical signs arising from cerebral metastases.

In all cases in this series the histological diagnosis had been established previously. In all cases given previous therapy, corticoid treatment was instituted only if there were unequivocal objective signs of progressing lesions. Patients who had received irradiation to the part under observation within the previous two months were excluded from drug trial. Blood transfusions, paracentesis, and symptomatic treatment were carried out as necessary, and in all cases of inadequate nutrition attempts were made to correct this by suitable diet. All objective criteria were assessed beforehand by diagrams, photographs, radiographs, and blood analysis. Subjective benefit was, however, also recorded, and improvement in appetite, gain in weight, and return to near normal life were observed in many cases. Improvement in the "performance status" of a patient was recorded as subjective improvement. Decrease of dyspnoea or of pain was recorded only as subjective improvement.

Clinical Results

The objective responses in this series of 154 cases are shown according to the site of active tumour, and according to whether prednisolone, prednisolone with nitromin, or dexamethasone was given (Table I). In the previously unreported series of 80 cases treated by prednisolone, objective response was noted in only 9 (11%) out of 80 cases. (In an additional nine cases the lesions under review, which had previously been growing, remained "arrested" for periods of three months or longer, but these are not included as objective responders.)

TABLE I.—Objective Response to Corticoids According to Metastatic Site—Three Series Separately Assessed

		Response in Proportion of Cases with Metastases				Proportion of Cases Responding
		Osseous	Local	Intra-thoracic	Visceral	
Prednisolone	80	2/36	3/48	2/33	2/11	9/80*
Pred. with nitromin	49	0/10	11/34	17/31	1/8	25/49
Dexamethasone	25	0/5	2/24	1/5	—	3/25

* In an additional 9 cases lesions were "arrested" for three months or longer.

The results of corticoid therapy in the whole series are considered from four points of view: (1) objective benefit in relation to dose level; (2) objective benefit in relation to age-group, menopause, and previous hormone sensitivity; (3) possible additive effect from the administration of alkylating agents; and (4) the relationship between benefit from corticosteroids and that from adrenalectomy.

Objective Benefit in Relation to Dose Level

Confusion has been created in this respect by several reports of castration combined with corticoid administra-

tion, and it is essential for our purpose that the results of administering corticoids alone should be clearly established in breast carcinoma. A review of previous reports (see above) shows that cortisone at a dose of 100–400 mg. daily gives a short-lived objective regression in breast cancer in 30 to 50% of cases, for periods of up to three months. Two of the papers emphasize that dosage of less than 100 mg. of cortisone daily is ineffective, and this was recently confirmed by Dao *et al.* (1961) in a special study.

Similar reports as for cortisone are noted for prednisolone at a dosage of 50–200 mg. daily (see above). Objective benefit is recorded in 18 to 29% of cases, but again rarely for longer than three months. However, it should be noted that prolonged dosage of 100–200 mg. of prednisolone daily may give rise to severe side-effects such as hypertension, diabetes, and hypokalaemia; and prolonged dosage of 50–100 mg. daily may give rise to glycosuria, dyspepsia, and mental changes.

It is therefore of interest to compare with these the results in a series of cases treated with only 30 mg. of prednisolone daily combined with triiodothyronine (Lemon, 1959) or with liothyronine (Gardner *et al.*, 1962). The former series claims the surprisingly high level of 48% of 31 cases to show objective regression, while the latter reports regression in 24% of 46 cases. (The first series is weighted by the factor that x-ray therapy or alkylating agents were added in many cases.) My series of 80 cases treated with 30 mg. of prednisolone daily gave objective benefit in only 11% of cases. The lower percentage could be explained by a difference in the selection of the sample or in the criteria of response, or might possibly be related to the use of added thyronine in the other series.

The side-effects resulting from three to six months' administration at this dosage were puffiness of the face and ankles, dyspepsia, and mild euphoria, and in only 2 out of the 154 cases were more serious complications noted—symptomless haematemesis in one and acute hyperexcitation in another.

On the other hand, doses below 25 mg. seem to be of much less value, as demonstrated in the following way. In those cases in which 30 mg. of prednisolone daily had been found to control the growth of soft-tissue lesions or visceral metastases, an attempt was made to cut the dose to 15 or 20 mg. daily. In practically every case where this was done signs of tumour regrowth were manifested, which was again controlled by increasing the dose to 30 mg. daily. It is therefore surprising that Van Gilse (1962) reports objective improvement in 37% of 109 cases treated by a "loading" dose, followed by a maintenance dose of 100 mg. of cortisone or 20 mg. of prednisolone daily. This may be accounted for by the fact that the vast majority of his "improvements" were in hypercalcaemia, pleural effusions, and anaemia.

From the foregoing reports there would appear to be no proved advantage, yet a considerable increase in side-effects, by using in all cases a dosage of prednisolone higher than 30 mg. daily. However, in my experience, exceptions requiring a higher "loading" dose include the patient with hypercalcaemia for whom 100 mg. of prednisolone daily is usually necessary to cause a fall in the serum-calcium level. This high dose-level may also be necessary in the other emergencies—in acute dyspnoea due to mediastinal or pulmonary metastases, and in coma due to cerebral metastases. In all cases dosage should be reduced to 60 mg. daily as soon as control of symptoms is achieved, and to 30 mg. daily for ambulatory patients. (It must be noted,

however, that even 20 mg. daily is not tolerated in some elderly patients with cardiac disease.)

Attempts to replace prednisolone with dexamethasone, betamethasone, or paramethasone in equivalent dosage were no more successful than with prednisolone itself (Stoll, 1960b). In cases of hypercalcaemia unresponsive to prednisolone, hydrocortisone in equivalent dosage was tried, but without success.

Dosage of corticoids was tailed off over one to two weeks in all cases. In addition, slow-acting corticotrophin (80 units tapered to 20 units daily) was given after two to three months' prednisolone administration in the early cases of the series, to counteract the depressant effect of corticoids on the adrenal cortex. Although no harm was noted when this was omitted, a case of acute adrenal insufficiency has been reported in the presence of intercurrent infection after long-continued prednisolone administration (Crawford and Forster, 1962).

Objective Benefit in Relation to Age-group, Menopause, and Previous Hormone Sensitivity

Table II illustrates the objective response to corticoids in the case of local soft-tissue growth in relation to the patients' "menopausal age." The results are divided into three groups, according to whether prednisolone, prednisolone with nitromin, or dexamethasone was given.

TABLE II.—Objective Response to Corticoids in Relation to Menstrual State—Three Series Separately Assessed

	Response of Cases in Proportion			
	Pred-nisolone	Pred. with Nit.	Dexa-methasone	Total
Premenopausal or <5 years postmenopausal	4/41	14/26	2/12	21/79
>5 years postmenopausal	4/39	11/23	1/13	16/75

It has been suggested (Lemon, 1959) that surgical ablation of ovarian function is an essential prerequisite to the successful use of corticoids in breast cancer. Nevertheless, I have previously reported objective response to corticoids in premenopausal cases (Stoll, 1960a), and 3 of the 37 cases showing objective response in this series were premenopausal. Gardner *et al.* (1962) have made a similar observation, although their figures suggest a greater effectiveness of prednisolone in older women. In our series and that of Van Gilse (1962) there is no suggestion that the patient's age in relation to the menopause bears any correlation to the likelihood of objective regression from corticoids (Table II).

An attempt is made to correlate response to corticoids with previous evidence of sensitivity to sex hormone in the same patient (Table III). It would appear that response to corticoids may be expected in a proportion of those cases previously not responsive to sex-hormone manipulation. This proportion does not significantly differ from the proportion responding in cases where there has been response to sex hormone. This is an important point made

TABLE III.—Objective Response to Corticoids in Relation to Previous Response to Sex Hormone Manipulation

	Response of Cases in Proportion			
	Pred-nisolone	Pred. with Nit.	Dexa-methasone	Total
Previous menopause, androgens, oestrogens beneficial	1/10	7/7	1/7	9/24
Previous menopause, androgens, oestrogens not beneficial	5/24	6/18	2/17	13/5

previously by me (Stoll, 1960a) and confirmed by Van Gilse (1962) and by Gardner *et al.* (1962).

It is therefore surprising that cortisone suppression of urinary calcium excretion has been suggested as a method of identifying hormone-sensitive breast cancer (Emerson and Jessiman, 1956). This test is still widely used, although Gerbrandy and Hellendoorn (1957) have pointed out that the decrease in calcium excretion following steroid therapy is often not associated with clinical improvement, as allowance must be made for non-specific calcium-retaining effects of steroids. In addition, hypercalciuria associated with malignant disease of various types, whether or not bone is involved, can be controlled by administration of corticoids (Plimpton and Gellhorn, 1956). This does not indicate a tumour sensitive to sex hormone, but reflects corticosteroid effect on mineral metabolism.

It is therefore important to note that corticoid administration may often be useful after failure of control by castration or testosterone administration in the younger patient, or by oestrogen administration in the older patient.

Possible Additive Effect of Alkylating Agents

The group of patients treated by a combination of prednisolone and nitrovin is considered separately from the rest of the series (Table I). Prednisolone (see above) and nitrovin (Stoll, 1956) have each been shown to induce objective benefit in the treatment of breast cancer when given alone. The theoretical possibility of delaying resistance in malignant cells by a combination of hormone and chemotherapy in breast cancer has been stressed (Stock, 1962).

Hochman and Ickowicz (1954) and McCarthy (1955) suggested the administration of cortisone at the same time as nitrogen mustard in tumour chemotherapy. A proportion of good results was reported by the former authors in the lymphomata, and by the latter author in 100 cases of advanced adenocarcinoma of various organs, including the breast. Synergism between corticosteroids and other ethylenimines was suggested also for cortisone and thiopeta in mammary tumours in mice (Wooley and Delmoro, 1955) and for cortisone and OPSA in human breast tumours (Curreri and McIver, 1956).

Nitrovin, unlike nitrogen mustard, has no vesicant action upon the skin or mucous membranes so long as it is well diluted. In addition, its action on the blood is somewhat slower than that of nitrogen mustard and recovery is more rapid. I previously reported the effect of combined prednisolone and nitrovin in 104 cases of solid cancer of all types (Stoll, 1960a), but it was only in the case of breast cancer that some additive effect appeared. Table I shows that this results mainly from the response of intrathoracic metastases, when the combination of prednisolone and nitrovin appears to be much more efficacious than prednisolone alone. It is therefore of interest that Escher and Kaufman (1961) state that the alkylating agents have their chief role in breast cancer in the treatment of lung infiltration, when both objective and subjective remissions may occur. Having noted, both in the literature and in our series, similar remissions from prednisolone, it is not surprising that the combination of the two drugs yields excellent additive results.

Although a truly synergic effect cannot be proved, it is now my policy to prescribe prednisolone and an alkylating agent immediately intrathoracic metastases are diagnosed in breast carcinoma. Their action appears to be independent of sensitivity to sex hormone and is rapid in its onset, although of comparatively short duration. Castration or

oestrogens, according to age-group, are instituted at the same time. Their effect (if the patient is going to show sensitivity to sex hormone) is considerably more delayed, but is in general much more prolonged. The combination of prednisolone and alkylating agent is tailed off after four to six weeks, when the sex-hormone control may be expected. This combination of methods gives, in my experience, objective remission in over 50% of cases in the presence of pleural or pulmonary metastases.

Comparison with Adrenalectomy

Some confusion has been caused by the use of the term "medical adrenalectomy," which some take to mean corticoid therapy alone but which others take to include also an x-ray or surgical ablation of the ovaries. The combined treatment is responsible for the excellent results reported by Nissen-Meyer and Vogt (1959), Brinkley and Kingsley Pillers (1960), and H. Atkins (personal communication, 1961). The role of the ovarian ablation is almost certainly a major factor in the combination, as it is, of course, also when combined with surgical adrenalectomy.

It has been suggested that the beneficial effects of adrenalectomy in breast cancer are due to the cortisone replacement therapy used after the operation. The paper by Dao *et al.* (1961) clarifies this issue. A series of 39 patients with advanced breast cancer were randomized into two groups—one group was treated by adrenalectomy and the other by cortisone acetate in the dosage used after adrenalectomy (maintenance level 50 mg. daily). The patients in the series were postmenopausal, and oophorectomy was not done in combination with either adrenalectomy or cortisone administration. Whereas none of the patients treated by cortisone at this dose level showed an objective response, 44% of the adrenalectomized patients showed such a response.

It has been suggested that the administration of corticoids, like adrenalectomy, causes suppression of adrenal oestrogen secretion. However, it has been demonstrated that even successful ablation therapy may be independent of oestrogen secretion (Scowen, 1958). The urinary excretion of oestrone, oestriol, and oestradiol is often not abolished by oophorectomy, adrenalectomy, or hypophysectomy in patients with mammary cancer showing a clinical response.

It is generally believed that a good clinical response by mammary cancer to corticoid therapy prognosticates a good subsequent response to adrenalectomy. This is not always true in my experience. Nor is the reverse true, as adrenalectomy may lead to a response even after failure of previous corticoid therapy (Dao *et al.*, 1961).

It is important to stress that, in the present series, relief of symptoms following corticoid administration generally lasted for a few months only. It was not as prolonged nor as complete as that reported in the remissions following adrenalectomy. Nevertheless, corticoid administration often brought marked subjective improvement in patients who were seriously ill. As mentioned before, it may hold their condition long enough for concomitant sex-hormone administration to show benefit, or it may improve their condition sufficiently to stand an operative procedure such as adrenalectomy or hypophysectomy. It should be mentioned here that previous corticoid administration does not appear to prejudice the problems of post-operative management of these cases.

Discussion

In the assessment of a palliative procedure in cancer it is important to consider three factors—the frequency

of palliation, the extent of palliation, and the duration of palliation. Most papers published to date on the benefit from corticoid therapy in breast cancer agree on one of these—the duration of palliation is short, approximately three months in the majority. The frequency of objective palliation in our cases was only 11%, although figures of 18 to 29% are noted in other critical series. The extent of palliation is also important, and it is my experience that in the case of soft-tissue metastases and lung infiltration regression is rarely complete.

These characteristics of the response to corticoid therapy, and its lack of correlation with previous response to sex-hormone manipulation, have led to the suggestion that the effect of corticoids in breast cancer is a local one upon the tumour bed. An anti-inflammatory action would decrease vascular permeability and oedema around the tumour. If this is the mode of control one would expect the clinical efficacy of a corticoid in mammary cancer to run parallel with its anti-inflammatory effect and to be equally as transient.

Natural corticosteroids exert certain distinct actions in the body which have not yet been clearly separated. These include protein katabolic, diabetogenic, and electrolyte-regulating properties, apart from A.C.T.H.-suppressing and anti-inflammatory properties. In the past 10 years new synthetic modifications of cortisone have aimed at strengthening its anti-inflammatory activity in relation to its other properties. The physician treating hormone-dependent cancer has, on the other hand, stressed the importance of the A.C.T.H.-suppressing property of corticoids—that is, the “medical adrenalectomy” or “medical hypophysectomy” view. Evidence is accumulating, however, that the anti-inflammatory property is responsible for much of the objective benefit reported after corticoid treatment of mammary cancer.

In the case of pulmonary, cerebral, or soft-tissue metastases it is suggested that corticoids may inhibit the tissue reaction around the tumour. Reduction in the size of pulmonary shadows, nodules, or nodes is the usual response, but complete disappearance of manifestations is rarely seen. A similar decrease in tissue oedema could explain the good response noted in 9 out of 15 cases of cerebral metastases from breast carcinoma (Kofman *et al.*, 1957). The same authors noted benefit in five out of seven of a series of non-hormone-sensitive primary and secondary brain tumours treated by prednisolone. Similar relief has

been obtained in 13 out of 14 patients with primary brain tumours treated by dexamethasone (Galicich *et al.*, 1961).

In the case of hypercalcaemia the control by corticoids may be by specific action on calcium metabolism (Gerbrandy and Hellendoorn, 1957), but pain relief is often associated. Graphs of urinary calcium excretion are shown for two patients with bone metastases. The first is of a patient in whom androgen therapy with fluoxymesterone (“ultandren”; “halotestin”) for eight months had given temporary control of pain, but later relapse was associated with a high urinary calcium output (Fig. 1). The administration of prednisolone 30 mg. daily caused a considerable fall in the serum and urinary calcium levels and again achieved full relief of pain. The second graph is of a patient who had been on prednisolone 30 mg. daily for three months, with partial relief of pain (Fig. 2). After

FIG. 1.—Urinary calcium excretion of a patient who received androgen therapy for eight months. Response to prednisolone.

FIG. 2.—Graph of a patient who had been on prednisolone 30 mg. daily for three months, with partial relief of pain. A rapid rise in serum and urinary calcium levels occurred on withdrawal of prednisolone, and pain increased.

withdrawal of prednisolone there ensued a rapid rise in the serum and urinary calcium levels, coincident with increase in pain symptoms.

The benefit from corticoid therapy in the presence of bone metastases can therefore be shown subjectively and biochemically, but, on the other hand, objective signs of recalcification of bone metastases are rarely seen. In this series they were noted in only 2 out of 51 cases with bone metastases and only after corticoids had been continued for periods of over 12 months.

In the majority of cases of breast cancer, therefore, the main benefit of corticoid administration is subjective, with reduction of pain and improvement of appetite and strength. This type of benefit, although seen in over 75% of cases, is, however, often associated with objective evidence of advancing disease. In any case, objective benefit is rarely seen for longer than three months; and it extended beyond nine months in only 3 out of 154 cases.

Summary

A series of 154 cases of advanced breast cancer treated by corticoids is reported. With objective criteria of response, only 12 of 105 cases treated by prednisolone or dexamethasone alone showed a response.

There appears to be no proved advantage in exceeding a dose of 30 mg. of prednisolone daily except for a "loading dose" in the emergencies of hypercalcaemia and cerebral and pulmonary metastases. A previous history of sex hormone insensitivity does not significantly influence response to corticoids, nor, in this series, does the age-group. Evidence is presented suggesting that the benefits of corticoid therapy may have a different mechanism from those due to sex-hormone control in breast carcinoma.

Objective response to corticoids is, in general, not as prolonged nor as complete as that following adrenalectomy, but subjective benefit is noted in a considerable proportion of cases. Combination with an alkylating agent gives remarkable, although short-lived, palliation of intrathoracic metastases.

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DIAGNOSIS OF HYPERPARATHYROIDISM IN PATIENTS PRESENTING WITH URINARY CALCULI

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Surgeons who treat patients for urinary calculi commonly regard the report of a normal serum calcium (Wooton and King, 1953) as sufficient evidence to exclude the diagnosis of hyperparathyroidism in the first instance. There are other biochemical tests (Howard *et al.*, 1953; Shaaf and Kyle, 1954; Nordin and Fraser, 1956; McIntosh *et al.*, 1958; Lloyd and Rose, 1958; Hyde *et al.*, 1960), but they are time-consuming or require specialized techniques, and may involve a stay in hospital for the patient: for these reasons they are frequently omitted.

In the urological unit of the Queen Elizabeth Hospital, Birmingham, the incidence of hyperparathyroidism in patients with urinary calculi during the five-year period 1955-9 has been 2.2%, and is lower than that reported from other centres (Albright and Reifstein, 1948; McIntosh *et al.*, 1958; McGeown, 1960). It is noteworthy, however, that no evidence of hyperparathyroidism has subsequently come to light in our patients after the initial treatment. In this unit, 11 mg./100 ml. has been taken as the upper limit of normal for the serum calcium concentration (Dent, 1956), and, moreover, we have felt that values between 11 and 12 mg./100 ml. are significant only when there are characteristic radiographic changes in the bones or there has been recurrent stone formation. To affirm this opinion it was decided: (1) to determine the frequency distribution of serum calcium and phosphorus values in the type of patient attending our clinics; (2) to review the frequency distribution of pre-operative serum calcium values in patients with renal stones and proved hyperparathyroidism who had been treated in the period 1955-9; and (3) to review a group of patients with urinary calculus disease seen during 1955-9 with serum calcium values greater than

the accepted normal but in whom subsequent investigations showed no evidence of hyperparathyroidism.

1. Frequency Distribution of Serum Calcium, Phosphorus, and Total Proteins

Peripheral venous blood samples were collected from 112 patients who were either attending the urological clinic and were mainly follow-up patients attending for cystoscopy, or were new patients attending for conditions other than urinary calculus; a few members of the medical, nursing, and secretarial staff were also included. A thin rubber-band tourniquet was kept in place for a maximum time of two minutes while the blood samples were obtained (Philpot, 1958). Serum calcium, phosphorus, and total protein concentrations were estimated. The serum calcium was estimated by the E.D.T.A./murexide technique using the E.E.L. titrator, serum phosphorus by the autoanalyser, and the total serum proteins by the method of Wolfson *et al.* (1948). The serum calcium values in this group of patients were found to range between 8.5 and 10.8 mg./100 ml., the serum phosphorus between 1.6 and 4.4 mg./100 ml., and the total proteins between 6.4 and 9.1 g./100 ml. (Fig. 1).

2. Pre-operative Serum Calcium Values in Cases of Renal Stone and Hyperparathyroidism

Eight patients with urinary calculus and hyperparathyroidism, proved by operation, were treated during 1955-9, and all eight were found to have pre-operative serum calcium values greater than 12 mg./100 ml. (Fig. 2).