Current Practice

Hormonal Management of Advanced Breast Cancer

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Breast cancer is the most common form of malignant disease to affect women in Europe and North America. About two in three of all cases will require palliative treatment in the later stages of the disease, and their management is therefore a relatively common problem. For this purpose hormonal therapy has a considerable advantage over treatment by surgery, radiation, or cytotoxic agents in that it does not significantly damage normal tissues. In addition, it is capable of controlling even widely disseminated breast cancer as a result of changes in the hormonal environment of the tumour. Unfortunately, in our present stage of knowledge, endocrine control of tumour growth activity is always temporary.

Castration, androgens, oestrogens, bilateral adrenalectomy, hypophyseal ablation by surgery or radiation, corticosteroids, and progestational and cytotoxic agents have each in turn been reported to cause regression of advanced breast cancer in a proportion of cases. To many physicians the place of each of these modalities in the management of the disease may appear to be largely a matter of individual preference because of the empirical nature of the treatment. Confusion is made worse by over-optimistic claims of cancerostatic activity for some of the new androgenic, oestrogenic, progestational, corticosteroid, and cytotoxic agents that have been synthesized in recent years.

There is as yet no specific sensitivity test available similar to that used in the antibiotic treatment of infection, but it is not widely realized that in spite of this specific guide lines are used for selecting the therapy most suitable for each individual patient.

The simple concept that hormone-sensitive breast cancer requires the presence of oestrogen to support its growth can no longer be maintained. The same tumour that shows temporary regression of growth after oophorectomy may, several years later, show regression after oestrogen administration. Certain observations suggest that significant change in the hormonal environment of the tumour may be more important in controlling the growth of breast cancer than the actual nature of the hormone causing the change. For example, in as many as one-third of patients whose tumours had regressed under oestrogen or androgen therapy it was found that when the tumour reactivates withdrawal of the hormone may be followed by a second regression. When the tumour then reactivates a second time it may again respond favourably to administration of the same hormone.

Sequential Therapy

It should be emphasized that only one in three of all patients with advanced breast cancer will show clinical evidence of a response to hormonal manipulation of any kind. Because of their very limited life expectation, it is essential to attempt to select not only those patients likely to benefit from such treatment but also the particular form of hormonal therapy to which the patient is likely to respond. Furthermore, as all forms of endocrine therapy involve some morbidity or deleterious side-effect, it is advisable to select the least noxious form of treatment first of all, possibly progressing with the advancing stage of the disease to more heroic measures.

Thus, for each patient the most suitable methods of endocrine therapy are selected in a particular sequence depending mainly on the age of the patient, the urgency of the symptoms, the site of metastasis, the history of previous hormonal response, and the general condition of the patient. Specific biochemical aids to this selection are also available, especially serial measurements of serum calcium, alkaline phosphatase, lactic dehydrogenase, and phosphohexose isomerase levels in the blood.[1]

In view of the controlling influence exerted by the anterior pituitary hormones over the other endocrine glands, it might be expected that the remission of tumour growth achieved by early hypophysial ablation would summate that achieved by preliminary trial of all lesser procedures. There is no evidence that it does so, as is shown below. Because of the morbidity of hypophysial ablation and the rarity of response to hormone administration *after* the operation, the majority of cancer therapists prefer the sequential attack, aiming to derive every possible remission from lesser procedures before proceeding to hypophysial ablation. Sequential endocrine management of advanced breast cancer is therefore conveniently divided into four stages—primary therapy, secondary therapy, major endocrine ablation, and post-ablation therapy.

Primary Therapy

In the management of recurrent or inoperable breast cancer, treatment of localized disease may be carried out by surgery or radiotherapy before endocrine therapy is considered. Mention should be made here of the excision of solitary skin nodules or a *mobile* mass of breast cancer recurrence, and of immediate decompression laminectomy in the presence of pressure by metastases on the spinal cord. Radiotherapy may be used to control the growth of localized metastatic nodules or nodes for periods of one to two years. The pain of localized bone metastases and the signs of pressure due to mediastinal or cerebral metastasis can usually be relieved by radiation therapy within a period of two to three weeks.

Therapeutic Castration

Castration is advised as the primary step in endocrine therapy in all premenopausal patients with recurrent or advanced breast cancer. (In some patients it will have been carried out prophylactically at the time of mastectomy.)

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Castration is advised also after the menopause if there is evidence of persistent oestrogen secretion by the ovary. Castration by surgery is preferred in the presence of urgent symptoms, such as those due to hypercalcaemia or to painful bone metastases, or if there are signs of lung, pleural, brain, or liver metastases. Surgical castration is advised also in cases in which the rate of tumour growth is rapid, as the earliest evidence of tumour regression appears within four to six weeks of the operation. Although radiation castration is just as effective in ablating ovarian secretion, it usually requires from two to three months to show its effect.

Additional androgen therapy (see below) started immediately after castration is advised by some in order to increase the likelihood of a response in the presence of bone metastases, or in the case of patients under 35 years of age. I agree with those who prefer to hold the additional therapy in reserve until it is clear that there is no response to castration, or until response to castration is lost.

Additional corticosteroid therapy (see below) is usually started before surgical castration in the presence of hypercalcaemia or in the very ill patient. Such therapy is also recommended immediately after radiation castration if insensitivity to sex hormones is shown in serial serum enzyme measurements, such as those mentioned above, or suggested by a short recurrence-free period after mastectomy.

Castration of the premenopausal patient is the simplest and most reliable endocrine method of achieving tumour regression in breast cancer. In large published series the tumour remission rate for surgical or radiation castration has been reported as being between 15 and 38%. The average period before tumour reactivation in such cases is between 10 and 25 months, and life is prolonged on an average from 18 to 22 months in responding cases compared with untreated cases.

There is a difference in the remission rate according to the site of the metastasis. Relief of pain from bone metastases and recalcification of lytic lesions in bone are the most likely to occur after castration. Objective evidence of regression of breast tumour, metastatic nodules, or nodes is less likely, and regression of visceral metastases in the liver, brain, lungs, or serous cavities is least likely. The patient's age may influence the remission rate in that tumour regression from castration is said to be less common in women under 35 years of age. Finally, the history of a long recurrence-free period after mastectomy increases the likelihood of response to castration.

"Medical castration" by androgens alone carries with it the complication of masculinization, and yields a much lower percentage and shorter duration of objectively demonstrable tumour remission. For these reasons androgens are better used as secondary therapy, and in patients responding favourably to surgical or radiation castration there is a 30% likelihood of a second tumour remission from androgen therapy later.

Oestrogen Therapy

Treatment with oestrogens is advised as the primary step in endocrine therapy in all patients in whom there is no evidence of oestrogen secretion by the ovary. In the older, postmenopausal woman oestrogen therapy yields a higher rate of tumour remission than any other method of endocrine therapy. Nevertheless, in the early postmenopausal years there is a danger of oestrogen therapy causing tumour growth exacerbation (and this is thought to be more likely if oestrogen secretion is still present). In this age period, therefore, oestrogen excretion assays are advised before a decision on endocrine therapy, but if the results of the estimation are equivocal oestrogens may safely be prescribed when five years have elapsed after the menopause. Under similar circumstances castration is advised for the first two years after the menopause, and androgen therapy between two and five years after the menopause. Whatever the number of years after the menopause, the presence of hypercalcaemia or liver or brain metastases calls for corticosteroids in preference to any other form of therapy.

In large published series the tumour remission rate for oestrogen therapy in advanced breast cancer has been reported as being between 29 and 37%. It should be emphasized that the tumour remission rate increases with the increasing number of years past the menopause. The average period before reactivation of breast cancer is 16 months, and life is prolonged on an average by 17 months in favourably responding cases compared with untreated cases. As in the case of castration, tumour response to oestrogen therapy is more likely in patients with a history of a long recurrence-free period after mastectomy.

The earliest signs of tumour regression appear within four to six weeks of initiating oestrogen therapy, and a trial cannot be regarded as unsuccessful unless maintained for at least two months. The healing of large ulcerated areas of tumour and the regression of metastatic nodules and nodes are common in elderly patients after oestrogen therapy, but relief of pain from bone metastases and recalcification of lytic metastases are seen less commonly. Regression of visceral metastases, especially of lung and pleural infiltration, is dramatic in some cases, and in responding cases there is a longer survival than in untreated cases.

Oestrogen therapy is usually given continuously, being maintained for as long as tumour control persists. In such cases withdrawal of the hormone when clinical response is lost will lead to a second regression of the tumour in 30% of cases. Alternatively, oestrogen therapy may be intermittent, administration being stopped when tumour regression is maximal. This method is particularly useful if drug administration is associated with serious side-effects, such as fluid retention and cardiac embarrassment.

The synthetic oestrogen stilboestrol is usually given at a dosage of 5 mg. t.d.s., or ethinyloestradiol may be given at a dosage of 0·5 mg. t.d.s. In the presence of preliminary intolerance to these agents, the more expensive mixture of natural conjugated oestrogens, Premarin, is usually well tolerated at a dose of 2·5 mg. t.d.s., and tolerance can then be built up to the other agents. Deleterious side-effects from oestrogen administration are seen in one-third of cases treated at these dosage levels, and include nausea, vomiting, anorexia, sodium and water retention, and urinary stress incontinence. Uterine bleeding is usually of a "withdrawal" type, but occasionally may be of a "breakthrough" character. With patience and selective medication a two-month trial of oestrogens should be achieved, as the results are so often rewarding in the elderly patient.

Secondary Therapy

Secondary hormonal therapy is used after primary treatment, either by castration or with oestrogen therapy, has lost its effect. Secondary therapy is achieved with androgens, corticosteroids, or progestational agents, depending on the site of metastasis, the history of hormonal response, and the urgency of the symptoms. Before secondary therapy is started there should be not merely subjective symptoms but objective evidence of advancing disease which is also reflected in the serial estimations of serum enzyme levels (see above).

Androgen Therapy

When tumour reactivation occurs after previous response to therapeutic castration a favourable response to androgens is likely in 30% of cases. In patients previously not responding to castration, response to androgen therapy is likely in fewer than 10% of cases, and in this group pituitary ablation (see below) may therefore be preferred in the presence of urgent symptoms. A trial of androgen therapy is useful also after previous response

to oestrogens has been lost, and a secondary response will occur in 22% of such cases. As mentioned previously, androgen therapy is preferred to oestrogen therapy as the primary method in patients between two and five years after the menopause, because of the possible danger of tumour growth exacerbation by the latter hormone.

In large published series the tumour remission rate from androgen therapy has been reported as being between 15 and 22%. The average period before reactivation of tumour is from 8 to 11 months, and life is prolonged on an average by 9 to 14 months in responding cases compared with untreated cases. As in the case of oestrogens, tumour response to androgen therapy is more likely with a history of a long recurrence-free interval after mastectomy. The tumour remission rate tends to increase with the increasing number of years past the menopause, and response to androgen therapy is unfortunately rare in the early postmenopausal years.

The earliest signs of tumour regression appear within four to six weeks of initiating androgen therapy, and a trial cannot be regarded as a failure unless continued for at least two months. Androgen therapy is especially indicated for the treatment of painful bone metastases, but in those associated with the presence of hypercalcaemia corticosteroid therapy is preferred (see below). It should be noted that recalcification of lytic bone metastases occurring after androgen therapy usually takes a minimum of three months to appear in radiographs. Regression of the breast tumour, metastatic nodules, or nodes is seen less commonly than with the use of oestrogen therapy. This applies also to regression of visceral metastases, including lung and pleural infiltration. Subjective benefit in the form of a gain in weight and an increase in appetite is, however, more common as a result of the anabolic effect of androgen therapy, as also is an increase in the haemoglobin level due to a stimulating effect on erythropoiesis.

The combination of an alkylating type of cytotoxic agent or radioactive phosphorus with androgen therapy is thought by some to increase the likelihood of favourable response in the presence of bone metastases. I agree with those who prefer to hold the additional therapy in reserve until it is clear that there is no response to androgen therapy, or until response to such therapy is lost. Androgen therapy is usually given continuously, being maintained for as long as tumour control continues. In such cases a withdrawal response may be seen in 10% of the cases when the hormone is stopped. Alternatively, androgen therapy may be intermittent, administration being stopped when tumour regression is maximal. This method is usually preferred because of the tendency to masculinization which is associated with prolonged androgen treatment.

Most of the early experience in the treatment of breast cancer by androgens was obtained from the use of testosterone propionate 100 mg. intramuscularly three times weekly. Longer-acting depot androgens such as Deca-Durabolin (nandrolone) and Primoteston-Depot (testosterone oenanthate) and testosterone implants are advocated by some, but these have the disadvantage that their action cannot be terminated abruptly if the patient develops hypercalcaemia. Signs of masculinization usually appear after more than three months' administration of any of these androgens at cancerostatic dosage, and include hirsutism of the face and body, hoarseness of the voice, and increase in libido. Administration of Vitandren (fluoxymesterone) in doses over 5 mg. q.i.d. has been shown to give a similar tumour remission rate to these androgens, but with the advantage of oral administration and with reduced signs of masculinization.

Corticosteroid Therapy

Corticosteroid therapy is often beneficial, even in the absence of previous response to primary therapy or if insensitivity to sex hormones is shown by serial serum enzyme measurements, as mentioned above. Corticosteroid therapy is almost always found to be beneficial in the presence of pain from bone metastases, hypercalcaemia, and lung, pleural, peritoneal, liver, or brain metastases. In the presence of hypercalcaemia subsequent major endocrine ablation therapy is indicated after control of the serum calcium level by corticosteroid therapy.

There is no correlation between the likelihood of benefit from corticosteroid therapy and that from previous sex hormone manipulation, and benefit is independent of age and whether the patient is pre- or postmenopausal. For these reasons it has been suggested that response to corticosteroids in breast cancer may be in part by an anti-inflammatory mechanism which decreases vascular permeability around the tumour and its metastases. This may be the reason for the rapid but temporary improvement occurring after therapy seen in the coma from cerebral metastases, or in the dyspnoea from pulmonary metastases.

Regression in the size of soft-tissue metastases and recalcification of lytic bone metastases are both usually partial in nature, and rarely last for longer than nine months. The combination of an alkylating type of cytotoxic agent (see below) with corticosteroid therapy is often found to be synergistic in the presence of brain, lung, pleural, or peritoneal metastases.

The great advantage of corticosteroid therapy is the feeling of well-being and the relief of pain it induces within a few days in the majority of patients treated. The steroid is especially useful in the treatment of patients who are too ill for major endocrine ablative surgery, or in those whose tumours are not sensitive to sex hormone administration.

Dosage is usually 10 mg. t.d.s. of prednisone or prednisolone, or 1·5 mg. t.d.s. of dexamethasone. Increasing the dose beyond these levels causes considerable increase in the danger from the side-effects, and elderly patients with heart failure may not tolerate even 20 mg. of prednisone or prednisolone daily. Nevertheless, a dosage of 20 to 30 mg. t.d.s. may be required in patients not responding to lower doses, and is almost always necessary in emergencies such as hypercalcaemia, acute dyspnoea due to pulmonary or mediastinal metastases, or coma due to cerebral metastases. Dosage should, however, be reduced to 10 mg. t.d.s. as soon as control of symptoms is achieved.

Progestin Therapy

Interest in the progestational agents in the treatment of breast cancer has been stimulated recently by the proliferation of these agents for the control of conception. There are three main chemical groups—derivatives of 19-nortestosterone, of 17α-hydroxyprogesterone, and of testosterone. The active progestins available differ in their oestrogenicity, androgenicity, pituitary-inhibiting properties, and metabolic activities. These factors should affect in theory the choice of an agent in the therapy of breast cancer, particularly in young women.

Tumour response has been noted to various forms of progestin therapy in 25% of a pooled series of breast cancer cases reported in the literature. Response in the case of bone or visceral metastases is rare, and therefore only patients with soft-tissue tumour are usually recommended for such therapy. The earliest signs of tumour regression usually appear within four to six weeks of starting therapy, and the average duration of response is less than nine months. "Withdrawal response" similar to that seen after oestrogen or androgen therapy has been noted also with progestin therapy.

Subjective benefit is common with these agents, associated with a gain in weight and an improvement in appetite, and deleterious side-effects are usually mild at the cancerostatic dosage reported. Progestin therapy is therefore indicated as an alternative to corticosteroids in patients with soft-tissue tumour metastases that have failed to respond to other forms of sex hormone therapy. It is interesting to note that in combination with small doses of oestrogen progestin therapy has

caused tumour regression in breast cancer even after hypophysectomy, whereas oestrogen therapy alone has never been shown to cause a response at this stage of treatment (see below).

Major Endocrine Ablation Therapy

It has been suggested that because the operations are more effective than hormone therapy bilateral adrenalectomy or hypophysectomy should be carried out at the first sign of recurrence in patients with breast cancer. This suggestion might appear to be supported by several large published series which have claimed tumour remission rates of 28 to 43% for bilateral adrenalectomy, 42 to 50% for hypophysectomy, and 28 to 37% for radioactive yttrium ablation of the pituitary. Nevertheless, after critical assessment of pooled series of cases, the Joint Committee of the American Medical Association[2] has reported that either hypophysectomy or bilateral adrenalectomy yields a 31 to 32% tumour remission rate, a postoperative mortality of 13 to 15%, and a mean duration of tumour remission after the operation of 21 to 22 months.

These remission rates are very little different from those of castration or oestrogen therapy, and their longer duration must be set against the not inconsiderable postoperative mortality rates as a result of major surgery. Furthermore, favourable response to hypophysial ablation may still be achieved in a high proportion of patients *after* a temporary response to castration or to sex hormone therapy, whereas the reverse is not true.

The choice between bilateral adrenalectomy and hypophysial ablation in one of its forms has been widely debated, but should depend in general on the experience of the specialists who are available. The relatively minor morbidity of the radioactive yttrium or transnasal methods of pituitary ablation is justified in patients who appear to be too ill for more major endocrine ablation therapy. The value of Bulbrook's urinary "discriminant function" for the selection of patients for major endocrine ablation is being investigated but has not yet been significantly proved in a *prospective* series.

Bilateral Adrenalectomy

Response to bilateral adrenalectomy is very much more likely in patients who have previously responded to castration, and adrenalectomy is not indicated in the absence of such a response previously. Response is also more likely the longer the recurrence-free interval since mastectomy. With regard to the effect on the response of the site of metastasis, tumour regression is most likely in the case of bone and soft-tissue metastases, less likely for those in lung and pleura, and least likely for brain, liver, and peritoneal metastases. (In fact, in the presence of large liver, brain, or peritoneal metastases the operation is contraindicated.) Relief of the pain of bone metastases is often dramatic after adrenalectomy but is usually transitory, and only in a minority is it associated with recalcification of lytic bone metastases. Its mechanism is uncertain.

There is no doubt that tumour growth remissions after bilateral adrenalectomy are longer and more complete than those that occur after corticosteroid therapy (sometimes described as "medical adrenalectomy"). Favourable response to corticosteroid therapy or its absence does not predict the likelihood of response to bilateral adrenalectomy. There is little doubt that added ovariectomy increases not only the proportion of patients responding to bilateral adrenalectomy but also the duration of tumour growth inhibition.

Hypophysial Ablation

Favourable response to subsequent hypophysectomy is very much more likely in patients who have previously responded to castration, and according to some authorities is almost certain in such cases. Surprisingly, no such correlation has been noted between favourable response to radioactive yttrium ablation of the pituitary and previous response to castration. As in the case of bilateral adrenalectomy, the longer the recurrence-free interval the more likely is a favourable response to hypophysial ablation. Response is very unlikely with recurrence-free periods of less than one year after mastectomy. Premenopausal patients and those over 60 years of age are more likely to benefit from hypophysectomy than are those patients in the intermediate age group, particularly those within six years of the menopause.

With regard to the effect on response of the site of metastasis, tumour regression from hypophysial ablation is most likely in the case of bone metastases, less likely for metastases in lung, pleura, and soft tissue, and least likely for liver, brain, and peritoneal metastases. As in the case of bilateral adrenalectomy, pain relief after hypophysial ablation is often dramatic but of short duration, and is not usually associated with evidence of recalcification of lytic bone metastases. It has been suggested that the relief of pain by hypophysial ablation may be due to an effect on the adjacent sympathetic plexus.

It is interesting to note that objective evidence of favourable response to hypophysial ablation by radiation may be achieved in patients who have not responded previously to either castration, sex hormone therapy, or bilateral adrenalectomy. The relatively minor morbidity of the transnasal radioactive yttrium methods of pituitary ablation may recommend their use in such cases, particularly if the patients are too ill for more major surgery.

Post-ablation Therapy

Localized radiation therapy is often beneficial in the presence of widespread disease that has ceased to respond to endocrine methods. Relief of pain from bone metastases, healing of malignant skin ulceration, and relief of pressure symptoms from cerebral metastases can usually be achieved by such therapy.

Hormonal Therapy

When the tumour reactivates after pituitary ablation there may be evidence of pituitary secretion persisting after the operation, and in such cases the possibility of sensitivity to hormonal therapy still exists. A course of progestin and oestrogen in combination (see above) has led to a response in some cases, particularly those with soft-tissue metastases. A course of the androgen fluoxymesterone has led to a response in others, particularly those with bone metastases. Other hormonal methods of therapy have not been proved of any value at this stage.

Cytotoxic Therapy

Intracavitary injection of thiotepa or of a similar alkylating agent can be used in the control of malignant pleural or peritoneal effusions, and may lead to the survival of such patients for a period of from one to two years. Systemic cytotoxic chemotherapy by thiotepa, cyclophosphamide, fluorouracil, or methotrexate has been reported in larger published series to lead to objective evidence of tumour remission in 20 to 30% of patients with advanced breast cancer. Dosage of such agents was discussed in the *British Medical Journal*.[3] Nevertheless, tumour growth regression from such agents is generally incomplete and lasts for only three to six months. The possibility of a partial, short-term remission must therefore be weighed against the danger and the morbidity of the toxic side-effects common to these agents.

Cytotoxic agents such as cyclophosphamide can also be given a trial in combination with androgens or corticosteroids (see above) *before* major endocrine ablation, dosage being taken only

to levels of *moderate* toxicity. There is no evidence that clinical benefit from cytotoxic agents in breast cancer runs parallel to the degree of the toxic side-effects.

Male Breast Cancer

Surgical castration is the most effective endocrine method of achieving tumour regression in male breast cancer. Subcapsular orchidectomy may be more acceptable psychologically than total orchidectomy, but enucleation of the testis must be complete to be effective. Radiation castration is not feasible in the male. Objective evidence of tumour regression has been reported in 68% of patients after castration—practically twice the response rate seen in females. Regression of soft-tissue metastases from male breast cancer occurs more commonly than does control of bone metastases.

According to the larger published series, the average duration of response to castration before reactivation of tumour is 29 months, but pain relief of bone metastases is sometimes maintained for several years. As in the female, the response to castration is better in males who show a longer recurrence-free interval after mastectomy. Prophylactic castration at the time of mastectomy is advisable in patients who are found to have invasion of the axillary nodes, in the hope of prolonging the recurrence-free interval.

Corticosteroid therapy is usually advised when tumour control by castration is lost. Palliation of symptoms results more frequently than after bilateral adrenalectomy or hypophysectomy in such cases, though occasional cases of tumour regression have been recorded after such major endocrine ablation. Oestrogen therapy also is occasionally effective in the management of advanced breast cancer in the male, and a tumour remission rate of 14% has been reported by one author.[4] As the primary method of therapy, it is not a reasonable alternative to castration, and, added to castration as primary therapy, it appears to add nothing to the tumour remission rate. Androgen administration, on the other hand, is said to exacerbate the growth of metastases from breast cancer.

To summarize, endocrine therapy is essentially a palliative procedure which is effective in a minority of patients. The average duration of tumour growth control and increase in survival from most methods is from 12 to 24 months. Several methods can be used sequentially with additive results, as more than one is often successful in the same patient. By using the most suitable means of hormonal therapy for each individual the extra months of life can be useful and pain-free. On the other hand, it may not be justifiable to aim at extra months of life at the expense of severe physical or mental disability, or at the risk of a high operative mortality rate.

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TODAY'S DRUGS

With the help of expert contributors we print in this section notes on drugs in common use.

Topical Corticosteroids

The treatment of skin diseases has been so transformed by the introduction of topical corticosteroids in 1952 that they now comprise 40% of the drug cost at a skin hospital and 4% of the total drug bill in the National Health Service. There are over 100 different preparations available as lotions, sprays, creams, ointments, and impregnated dressings with and without various other agents. The practitioner has to decide not only whether steroid therapy is indicated but also which of the many products to prescribe.

The prime action of topical corticosteroids is still under study, but it is likely that by stabilizing the lysosome membrane in cells in the skin they reduce the inflammatory response and so relieve the erythema, oedema, inflammatory infiltrate, and any concomitant pruritus. Since the effect is only suppressive, relapse occurs if the cause of the inflammation is still acting when the therapy is withdrawn. If the cause is infective, the natural defence mechanism will be impaired and the condition aggravated, though initially some of the symptoms may be relieved.

Choice

There have been three generations of corticosteroids for use on the skin. Hydrocortisone held the field from 1952 to 1959; others of comparable strength, prednisone, prednisolone, betamethasone, and dexamethasone, had no advantage, and all these were superseded in 1960 by the second generation, the halogenated steroids, triamcinolone,[1] flumethasone[2] and flurandrenolone,[3] four to six times as potent as hydrocortisone in their action on the skin. These last three are recommended when a weaker steroid is required. These were followed in 1962 and since by the third generation, 10 to 20 times stronger than hydrocortisone; first came fluocinolone,[4] then betamethasone 17-valerate,[5] fluocortolone,[6] fluorometholone,[7] and beclomethasone.[8] The concentration of steroid in topical preparations varies from as little as 0·01% of triamcinolone to 2·5% of hydrocortisone, but the levels are chosen for their optimum effectiveness. In some products the concentration of steroid is lower than optimum[9,10]; this reduces both efficacy and the risk of side-effects while still producing sufficient therapeutic effect. One product is available in a higher concentration (0·2% fluocinolone acetonide cream[11]) for use in special disorders.

These products differ little in price, because the steroid comprises a small part of the total cost. Nevertheless, it is wiser to use the weakest preparation which will bring adequate relief, and keep the more potent remedies in reserve. If large areas have to be treated the risk of systemic and local absorption is reduced if a weaker preparation or a diluted potent one is used. When an added chemotherapeutic agent is required, clioquinol (usually designated by the suffix C) is preferred because it has a wide spectrum of activity against bacteria, fungi, and candida, and it is less likely than most other agents to produce allergic contact eczema. Chlortetracycline is an alternative, but its range of activity is less than clioquinol, and secondary candidiasis is more likely; hexachlorophane is also available, but only in products[6] containing lanolin. Clioquinol unfortunately stains clothing slightly yellow, but it does wash out in time; it should not be used on the scalp if the hair is white, when neomycin or hexachlorophane products are preferred.