Summary

This thesis describes one clinical and three endocrine studies with medroxyprogesterone acetate (MPA) in postmenopausal women with advanced breast cancer. In the clinical study, the therapeutic effect of MPA and tamoxifen are compared. In the endocrine studies, the effect of MPA on the pituitary adrenal axis as well as its mechanism are studied.

Chapter I is an introduction and gives a general view of hormonal therapy in metastatic breast cancer. The frequent incidence of breast cancer is emphasized as well as the fact that two thirds of the patients eventually will require systemic palliative treatment. The choice between hormonal and cytostatic therapy depends on a number of conditions: age, disease-free interval, tumor progression rate, predominant site and extent of metastases, hormone receptor status and response to prior therapy. The various hormonal modalities are successively discussed in historical sequence. On the one hand there are the so-called ablative treatments: oophorectomy, adrenalectomy and hypophysectomy. On the other hand the following additive therapies nowadays are available: androgens, estrogens, progestins, corticosteroids, tamoxifen, aminoglutethimide and LHRH-analogues. Their mode of action, effectiveness and side-effects are discussed. Finally the relation between dose and response is regarded. This relation does exist for the progestins and possibly for estrogens and aminoglutethimide, but is not evident in the other agents.

Chapter II describes the results of a prospective randomised multicentre phase III trial comparing the response to treatment with oral high-dose MPA and tamoxifen in previously untreated postmenopausal patients with advanced breast cancer. MPA in a dose of 900 mg daily (300 mg t.i.d.) yields a remission rate of 44% and appears to be at least as effective as 40 mg tamoxifen daily (20 mg b.i.d.) with a remission rate of 35%. The duration of remission and the length of survival is not significantly different in both treatment groups. In patients with predominant osseous metastases, as well as in a group of patients over 70 years, MPA has a higher response rate than tamoxifen. After disease progression, therapy was changed to the other of the two drugs. As second treatment MPA appears to give a significantly higher response than tamoxifen. MPA has more side effects, which are sometimes severe. Consequently high-dose MPA will be reserved as the second therapy after tamoxifen. However, in case of predominant osseous metastases and in older patients it has to be considered as the initial treatment.

In chapter III the effect of high-dose MPA on the pituitary-adrenal system is described. Postmenopausal women with advanced breast cancer, treated with MPA in a dose of 900 mg daily, are compared with (still) untreated postmenopausal breast cancer patients. In most of the MPA-treated pa-

tients the cortisol levels are lower. However, ACTH-levels are not clearly increased, nor decreased, suggesting a simultaneous direct inhibition of ACTH-release by MPA. The levels of the androgens androstenedione and DHEA-S are suppressed to a similar extent as cortisol. Furthermore, a significant fall of LH- and FSH-levels is observed, while prolactin and growth hormone do not change. It seems reasonable to assume that high-dose MPA has a direct, but incomplete suppressive effect on the adrenal function, combined with a negative effect on ACTH-release.

Chapter IV shows the endocrine effects of direct and indirect adrenal stimulation in MPA-treated postmenopausal breast cancer patients. One group of patients is treated with 900 mg MPA (300 mg t.i.d.) orally, a control group is not (yet) treated. After direct adrenal stimulation with Synacthen the stimulated cortisol levels in the MPA-group are lower than in the control group. The stimulated levels of androstenedione and 17-OH-progesterone are also less high in the MPA-patients compared with the control patients, but to a lesser degree than the cortisol levels. Indirect adrenal stimulation with metyrapone leads to a greater decrease of cortisol levels and a greater increase of ACTH-levels in the MPA-group compared with the control group, but to a relatively small rise of 11-desoxycortisol, androstenedione and 17-OH-progesterone. Thus there is an impaired adrenal response to direct and indirect stimulation in MPA-treated patients. The higher ACTH-levels, together with lower cortisol, after metyrapone in the MPA-patients, indicate that a direct suppression of ACTH by MPA is not the only cause of adrenal blockade. The small increase of 11-desoxycortisol, despite a sufficient rise in endogenous ACTH-levels, suggests that this partial adrenal blockade is also located in the adrenals themselves. So the results of both stimulation tests indicate a direct, but partial inhibitory effect of MPA on the adrenals.

In chapter V the relation is discussed between different doses of MPA, the plasma levels attained, and the extent of adrenal suppression. Apart from a control group of patients, three other groups were formed, who received doses MPA of 300 mg (group I), 600 mg (group II) and 900 mg (group III) respectively. A significant difference in plasma concentration of MPA is found between groups III and I. With a dose of 900 mg the median level of MPA is higher than 100 ng/ml, which has been advised as a minimal level for clinical effect. However, there appears to be a considerable variation in individual MPA-levels within each group. Several explanations for this are discussed. Significant differences in suppression of the adrenal steroids cortisol, DHEA-S and androstenedione, as well as of oestrone, are found only between the groups I and III, but not between the other groups. Cortisol levels higher than 150 nmol/l appear to be a reliable indicator of insufficient MPA-levels. However, low cortisol levels do not always indicate sufficient MPA-levels. There seems to be a negative but weak correlation between MPA-levels and the adrenal steroids, but not between MPA and oestrone

levels. However, in the MPA-treated group a positive correlation between androstenedione and oestrone is found. Suppression of oestrone, which is the most important estrogen in postmenopausal women, may be responsible for the tumor-reducing effect of MPA in hormone dependent breast cancer. Doses of 900 mg MPA result in a stronger adrenal suppression than doses of 300 mg and thus lead to lower androstenedione and oestrone levels. In this way the enhanced efficacy of high doses MPA in metastatic breast cancer may be explained.

Conclusion. In postmenopausal patients with advanced breast cancer, oral high-dose MPA has an efficacy comparable with that of tamoxifen. Generally MPA will be reserved as a second treatment after tamoxifen, because it has more frequent side-effects and is more effective following tamoxifen, while tamoxifen given after MPA has a poor therapeutic effect. MPA results in an incomplete direct adrenal suppression and has a negative effect on ACTH release. High doses of MPA bring about higher plasma levels and a greater adrenal suppression than lower doses. The fall of androstenedione as the main source of postmenopausal oestrone may be a possible mechanism for the enhanced effect of high doses of MPA in breast cancer.