It seems apparent that the endocrine treatment of metastasizing mammary cancer has in some way reached a point from which it is not easy to make advances. This opinion is further supported by the failure of a number of recent investigations to demonstrate a significant relationship between clinical improvement and a decrease in the oestrogen production, measured as the urine secretion or as a biological effect in the vaginal smear (Overbeek & de Visser 1957, Segaloff 1958, Hiisi-Brummer et al. 1960, Mc Allister 1960). The traditional treatment includes castration, androgens, oestrogens, cortisone, adrenalectomy and hypophysectomy. The frequency of favourable responses with different types of endocrine treatment seems to be established within known limits. The duration of the clinical remission produced also seems to be clear. Important recent contributions are the suggestion to use cortisone simultaneously with castration, as is recommended by Nissen-Meyer (1960), and the recent study by Atkins (1960) showing the superiority of hypophysectomy to adrenalectomy. In this situation the rôle played by the nortestosterone derivatives is of considerable interest. These compounds have, as is well known, a stronger anabolic and less virilizing effect than the androgenic hormones. They are easier to administer and show fewer and milder side effects. This report concerns experiences with norandrostenolone phenylpropionate and norandrostenolone decanoate. Results with the first named preparation having the trade name Durabolin have already been reported (Nowakowski & Parada 1959, Van der Werff 1958, Malmio et al. 1960, Hortling et al. 1960). At the Homburg symposium on the treatment of mammary cancer I reported some preliminary impressions of the use of nortestosterone decanoate (Deca-Durabolin).

Now I intend to give more detailed results of the use of Durabolin, laying special stress on the effect of this drug as compared with the effects of other endocrine methods and thus to suggest a place for the nortestosterone derivatives.
in relation to the other methods used. The results of the use of norandrostenolone decanoate in 48 patients suffering from metastasizing mammary cancer is also reported.

These results are part of a larger study soon to be published concerning endocrine treatment of 436 patients with metastasizing mammary cancer. Altogether these patients received 888 endocrine treatment courses. The results were uniformly interpreted by a radiologist in collaboration with myself being a specialist in internal medicine and endocrinology. 47 patients were not included because it was later shown that the treated metastases were not in an active stage or that a clinical result could be mainly ascribed to a simultaneous X-ray treatment. Objective remissions or arrest of the disease were both accepted as a favourable clinical effect but a purely subjective effect was not. An objective remission was established visually, by X-ray investigation, by disappearance of normoblasts from the peripheral blood or by a long-standing increase of the general well-being with a decrease of the blood sedimentation rate and/or disappearance of anaemia. Clinical arrest means in this study a standstill or a marked slowing down of an otherwise progressive course of the disease accompanied by improved clinical well-being. Cases in which it was not possible to exclude an auxiliary effect of X-ray treatment are put in a separate group. As a rule, endocrine treatment was administered when only a slight benefit, if any, was to be expected from X-ray treatment. The endocrine therapy went on as long as the clinical effect lasted and for at least one month before a negative effect was admitted. Endocrine manoeuvres that had to be interrupted because of side effects caused by the therapeutic agent, were included among the negative cases.

In table 1 the results of the use of norandrostenolone phenylpropionate are shown. The treated cases are divided into sub-groups depending on the order in which this drug was given in relation to other endocrine treatment. The figures differ somewhat from those previously reported as some of the cases previously included as favourable responses later proved not to be active metastases or the subsequent course of the disease showed that the therapy was in fact a failure. This also shows that the evaluation of a clinical effect in metastasizing mammary cancer is sometimes very difficult. On the whole, however, the results in this table are comparable to previous figures with regard to the frequency and duration of favourable responses to norandrostenolone phenylpropionate. The table also shows that the results are rather good even when Durabolin is administered after other previous therapy has lost its effect.

The duration of the favourable effect is recorded in table 2. On average the duration was 11 - 12 months. This is about the same duration as has been reported
The results of treatment with norandrostenolone phenylpropionate in 126 cases.

Table 1

<table>
<thead>
<tr>
<th>Objective improvement</th>
<th>Arrest</th>
<th>Poor result response in per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st manoeuvre</td>
<td>Clear cases</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>X-ray effect possible</td>
<td>4</td>
</tr>
<tr>
<td>2nd manoeuvre</td>
<td>Clear cases</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>X-ray effect possible</td>
<td>5</td>
</tr>
<tr>
<td>3rd manoeuvre</td>
<td>Clear cases</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>X-ray effect possible</td>
<td>1</td>
</tr>
<tr>
<td>4th manoeuvre</td>
<td>Clear cases</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>X-ray effect possible</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>12</td>
</tr>
</tbody>
</table>

Hypophysectomized patients

12

Mean duration of a favourable clinical effect induced with nortestosterone derivatives and androgens. Time in months.

<table>
<thead>
<tr>
<th>1st manoeuvre</th>
<th>No. of cases</th>
<th>No. of later manoeuvres</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norandrostenolone phenylpropionate</td>
<td>7</td>
<td>12.3</td>
</tr>
<tr>
<td>Norandrostenolone decanoate</td>
<td>9 (all courses)</td>
<td>8 mths</td>
</tr>
<tr>
<td>Androgens</td>
<td>18</td>
<td>11.7</td>
</tr>
</tbody>
</table>

by several authors for androgen therapy, or somewhat longer. In my own series of androgen-treated patients the objective remission lasted about the same time or 10.7 months. The series are not quite comparable as Durabolin was perhaps administered during a later stage of the disease. The side effects connected with the use of Durabolin have been previously reported. If one considers only the more disturbing side effects which the patient himself has reported, only 15 patients
complained of side effects. These were skin eruptions in 4 patients, hoarseness of the voice in 4, unwellness, nervousness and dizziness in 3, oedemas in 2, local infiltration in 1 and aching in the joints in 1. In 6 patients a slight increase of the serum calcium was occasionally recorded but without clinical symptoms of hypercalcaemia. The treatment had to be interrupted in only 3 patients, because of furuncles in one and nausea in connection with the injections in two. Unfortunately, the serum calcium could not be studied in these patients as they lived far away.

The results of the treatment with Durabolin are also shown in Fig. 1 together with the results we obtained with other types of endocrine treatment. From this figure one may see that the effect is rather good even when Durabolin was administered after other treatment courses. A comparable effect was seen only when hypophysectomy had been performed. By contrast, castration, androgens and oestrogens were much less effective when used after other previous therapy. This should indicate that Durabolin is probably the treatment of choice as an interval therapy after the effect of castration, cortisone plus castration or oestrogens have subsided. The androgens seem to have played out their rôle as a routine method in the endocrine treatment of metastasizing mammary cancer when one considers the high frequency of side effects with this hormone and the fact that castration, especially when administered together with cortisone, is a superior method. Durabolin is also effective after androgen therapy, as has been shown in a

Fig. 1

Results of different types of endocrine treatment for mammary cancer.
previous report (Hortling et al. 1960). On the other hand, hypophysectomy also gives better results than other methods, when used after the other previous endocrine therapy, with regard to both frequency and duration of remissions or arrests. Durabolin is not effective in hypophysectomized patients. An interesting feature is the number of lung metastases that respond favourably to Durabolin (Hortling et al. 1960). This may indicate that it is not only the anabolic action that is exerted when remission occurs.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Favourable response</th>
<th>Poor response</th>
<th>Favourable response in per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st manoeuvre</td>
<td>3</td>
<td>5</td>
<td>37.5</td>
</tr>
<tr>
<td>2nd-5th manoeuvre Clear cases</td>
<td>9</td>
<td>19</td>
<td>32.1</td>
</tr>
<tr>
<td>X-ray effect possible</td>
<td>1</td>
<td></td>
<td>34.5</td>
</tr>
<tr>
<td>Hypophysectomized patients</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Clinical results of treatment with norandrostenolone decanoate in 39 patients.

Norandrostenolone decanoate was used in the treatment of 48 patients suffering from metastasizing mammary cancer. The effect could be evaluated in 39 patients along similar lines as were used when Durabolin was concerned. The results are presented in Table 3. The frequency of favourable results corresponds roughly to that seen with Durabolin. The duration of the favourable effect was on average more than 8 months (Table 2) as the effect was still continuing in some patients. In 3 patients not included in the table a promising subjective effect could be observed. It is thus possible that the duration of the clinical effect with Deca-Durabolin is shorter than is seen with Durabolin.

With regard to the location of the metastases, a good effect on norandrostenolone decanoate was observed in all the different sites except the brain, where no metastases were treated. Thus out of 13 favourably responding cases the disease was mainly located in the lungs in 5 cases, in the bones in 2 cases, locally or in the lymph nodes in 3 cases and twice in some internal organ. Once a palpable mass the size of a hen's egg connected with the hard, somewhat enlarged liver without signs of gall bladder disease, disappeared. The palpable liver border moved upwards.

When the effect of norandrostenolone decanoate was compared to the effect seen with previous therapy the following observations were made. 17 patients had previously received Durabolin with good effect in 5 of them. 6 of these 17 patients responded favourably to norandrostenolone decanoate, two of whom had also responded well to Durabolin.
No side effects were reported by the patients during norandrostenolone decanoate therapy.

The therapeutic doses of androgens (150 mg testosterone phenylpropionate weekly), of norandrostenolone phenylpropionate (25 - 50 mg weekly) or of norandrostenolone decanoate (25 mg every third week), correspond roughly to each other with regard to their anabolic properties (1.5 : 1 : 0.8 calculated from available data), whereas their androgenic properties differ greatly from each other. It seems that if the androgenic effect in a therapeutic dose of androgens equals 6, the androgenic effect of norandrostenolone phenylpropionate equals 1 and the corresponding effect of norandrostenolone decanoate is close to 0.1. This opinion is reached when the data in available reports are compared (Nowakowski & Schmidt 1959, Overbeek & de Visser 1957). With this calculation in mind, a comparison is made in the next diagram of the clinical usefulness of androgens, Durabolin and Deca-Durabolin (Fig. 2).

![Diagram](image)

**Fig. 2**
Comparison of the clinical effect of androgens, norandrostenolone phenylpropionate (Durabolin) and norandrostenolone decanoate (Deca-Durabolin).

One may draw the conclusion that the androgenic effect is not the deciding factor for the clinical effect on the metastases; on the contrary it may be a disturbing factor. Even if there are apparently no great differences between the anabolic preparations used, one dare not say anything about the relations between the anabolic potency and the therapeutic effect. The biological oestrogenic effect has been followed during the different treatment courses. The results are seen in Table 4. It was of some interest that the parallelism between a positive clinical effect and a decrease in the biological oestrogen effect was closer in Durabolin treated patients than in androgen treated patients. During the course of treatment a rise in the oestrogen effect was most common when androgens were concerned, less common when norandrostenolone decanoate was used.
Table 4

Correlation between changes in the level of the oestrogen effect and the clinical response to endocrine therapy.

<table>
<thead>
<tr>
<th>Number of cases examined</th>
<th>Decrease of oestrogen effect. Per cent of investigated cases</th>
<th>Increase of oestrogen effect. Per cent of investigated cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Favourable response</td>
<td>Poor response</td>
</tr>
<tr>
<td>Androgens</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>92</td>
<td>71.4</td>
</tr>
<tr>
<td></td>
<td>(3/29)</td>
<td></td>
</tr>
<tr>
<td>Norandrostenolone</td>
<td>51</td>
<td>61.9</td>
</tr>
<tr>
<td>phenylpropionate</td>
<td>(1/21)</td>
<td></td>
</tr>
<tr>
<td>Norandrostenolone</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>decanoate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Correlation between changes in the level of the oestrogen effect and the clinical response to endocrine therapy.

Ethylestrenol was used and not seen at all in the few cases where this reaction was studied during norandrostenolone decanoate therapy.

In conclusion it may be said that the norandrostenolone derivatives seem to be well suited for interval treatment in the endocrine therapy of metastasizing mammary cancer. This holds especially true with regard to Durabolin, whereas our experience with norandrostenolone decanoate is still too limited. As the side effects of norandrostenolone decanoate are quite insignificant in comparison to those seen with Durabolin - where they are also of minor importance - a further therapeutic trial with norandrostenolone decanoate is indicated. The fact that norandrostenolone decanoate was also effective in cases that had previously been treated with Durabolin seems to indicate that it may be worth-while to try to develop other agents of the same type as the nortestosterone preparations used hitherto. It would also be of value to gain further information as to what is the effective therapeutic property of these drugs.

Ethylestrenol.

Finally I want to report on some results obtained with ethylestrenol. Ethylestrenol was used on a series of 36 patients, on whom it seemed worth-while to try an anabolic agent. The effect could be evaluated in 31 of them. The dose used was 4 mg orally daily either 1 mg 4 times daily or 2 mg twice daily. The time of administration was 5 - 10 weeks.
In 16 of the patients no favourable effect was apparent: 11 of them could be grouped under such headings as general bad health, arteriosclerosis, old age and neurosis. One patient had nephrosclerosis, one patient used cortisone regularly because of asthma and she had a hemiplegia some months before the treatment with ethylestrenol, one has parkinsonism and one alopecia totalis at the age of 15. All patients except two were over 50 years old.

In 16 patients a clear favourable effect was seen which could not be ascribed to other treatment. Two of them suffered from anorexia nervosa. The weight increased by 2½ kg in both. One had been treated by myself for three years without any similar effect. A menstruation reappeared during the treatment without the use of female hormones. In one case of osteogenesis imperfecta (11 years old) spells of fainting disappeared, three patients had osteoporosis, one after long term use of cortisone, another was 96 years old and had been bedridden with severe backache. He got up again and the pains disappeared. One 69 year old female patient with persistent hypercalciuria and pain showed general improvement during treatment and less pain. One patient with renal insufficiency probably with an infectious basis, improved in general health and the serum creatinine decreased from 2 to 1.8 mg%. A 15 year old boy who was only 151 cm in height grew 2 cm during the two months the treatment lasted. Two patients with emphysema and arteriosclerosis showed improvement in general health. Two cases with longstanding hemiplegia showed improvement in the strength of the paralyzed limb and could move it better than before. The same was seen in a patient suffering from rheumatoid arthritis.

Apparently diffuse disorders were commoner among the negative cases whereas the favourable responding group included more cases in which a negative balance of the calcium and protein reserve was probable.

As a rule no side-effects were seen. One patient, 63 years old, told of a transient "spring feeling" that she had not had for many years, another of transient tingling in the skin. In none of the patients was hirsutism or hoarseness of the voice observed. The treatment in these cases did, however, last longer than 10 weeks in any case. One patient experienced nausea 45 minutes after the intake of two tablets but not when she used only one.

The preliminary general impression of ethylestrenol is that it is a potent anabolic agent that is probably of clinical value.

Acknowledgement

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REFERENCES


DISCUSSION

Tausk: Thank you very much, Dr Hortling, this paper is now open for discussion.
Bierich: I should like to ask whether I understood you rightly regarding the observation that Durabolin was not effective in hypophysectomized patients. This may be similar to the things we heard yesterday in an entirely different field mentioned by Dr Prader, regarding the pituitary dwarfs, who did not respond very well to anabolic agents. Have you any explanation for this observation?
Hortling: I do not think that I can give you any explanation. I believe that hypophysectomy has thoroughly exhausted all the endocrine possibilities. This is also the reason why I think it is better to use this method as a last resort.
Tausk: May I say something here with regard to this discussion? Yesterday it was suggested that in order to get a beneficial anabolic effect from these steroids, growth hormone is needed. It is my impression that we are dealing here with something fundamentally different, because in those cases what was needed was a kind of synergistic effect. We know that growth hormone and steroids will both be anabolic and that they apparently need each other. Here we believe that the pituitary would, if anything, promote the growth of the carcinoma and the steroid is supposed to inhibit it. Nobody knows exactly what is the anti-cancerous effect of these drugs. Probably there are stimulating effects from the pituitary furthering the development of mammary carcinoma, either directly on the tumour or through the gonads. This may well be one of the main points of attack of these steroids. This is of course speculation.
Kopera: Could it be that the results reported by Dr Hortling are more or less an answer to the question put forward by Dr Prader yesterday as to whether a dissociation between androgenic and anabolic effect has been established in man? I think one could draw the conclusion from the results of Dr Hortling that an androgenic property is responsible for the therapeutic effect. They seem rather to demonstrate - at least in adults - something like a dissociation of action.

Prader: I am getting more and more confused about the anti-cancerous effects. Dr Kopera, I gather you imply that it is an anabolic effect. Prof. Tausk suggested that it is a gonadotrophin suppressing effect.

Tausk: I am not at all sure, Dr Prader, whether it is the gonadotrophin. What I said was, it looks as though the pituitary might have a cancer-promoting effect in these cases and that this effect could be exercised by the pituitary through different mechanisms. There are indications that prolactin from the pituitary will directly stimulate the mammary gland and carcinoma. On the other hand there is an indication that it works through the ovary and maybe growth hormone has something to do with it. All I want to say in a vaguely speculative way is that these steroids may somehow need the pituitary which seems to hold a position in this mechanism.

Overbeek: I should like to add a few words with respect to this discussion. Firstly, I do not believe that the anabolic effect is responsible for the anti-tumour effect as seen in mammary carcinoma. I think, that what Dr Hortling has said about the correlation with anti-oestrogenic effect and what Prof. Tausk has said about the pituitary inhibition is probably far more important. The latter may very well explain why these hypophysectomized patients respond less, although they may still respond on account of the anti-oestrogenic effect.

Bierich: In this case of course, the more androgenic preparations should have a better effect but they do not have. Is it not the case that androgens have a more depressing effect upon the prolactin, upon the pituitary and upon the gonadotrophin production, in comparison with the pure anabolic hormones?

Overbeek: There is a difference. We have been looking for it but we could not find such a difference between Durabolin and Deca-Durabolin. Deca-Durabolin, at least in the animal experiments, is less inhibiting to the pituitary and less anti-oestrogenic than Durabolin. So we looked to see whether there might be a difference, whether Durabolin might be better than Deca-Durabolin in these cases, but it was not however the case.

IJzerman: I think that at least you may say this: whether the beneficial effect is caused by the pituitary inhibition or by some other mechanism there are some very clear indications from Dr Hortling’s work that it is not linked to the androgenic effect. I think this is the point we want to make and I think this is also the point Dr Kopera wanted to bring forward: that it is not linked to the androgenic effect so that therefore there is a dissociation. Now whether it is a dissociation between
the anabolic and androgenic effect or between the anabolic and other effects may be obscure, but it seems certain that there is a dissociation in these various activities.  

Kopera: Relevant to this are also the observations on several patients under Durabolin treatment and in whom a good anabolic effect was obtained together with an androgenic side effect during the course of long term treatment. After the patients were switched over to Deca-Durabolin, the same anabolic effect continued to be observed, whereas the virilizing effect diminished and sometimes disappeared completely. Thus I think there must be a dissociation between the two actions.

Nowakowski: I would like to ask Dr Hortling what he thinks about the action of oral anabolic steroids in mammary cancer? I mention this point because some people in the U.S.A. are very afraid of using long-acting steroids.

Tausk: Do you mean they are afraid to use them because when long-acting steroids are administered and a hypercalcaemia occurs you cannot combat it?

Nowakowski: Yes, and you do not run that risk with oral preparations. They are short acting and you can immediately discontinue the treatment.

IJzerman: The only reason that the American cancerologists are so much opposed to long-acting androgens is the fear of inducing hypercalcaemia. Until now, (with the exception perhaps of the one case reported on here) we have had no knowledge of a single case in which Durabolin was used and where there was evidence of induced hypercalcaemia. This I think does away with the arguments against long-acting preparations in mammary carcinoma.

Nowakowski: Yes, I agree. I used to say that but they did not accept it.

Hortling: I think it is a particularly favourable property in the treatment of mammary carcinoma that one can give such long-acting injections as the patients are often very ill and do not like to take tablets at all. It is sometimes difficult to evaluate the results of these oral preparations and also the side effects are so small that there is practically no chance of hypercalcaemia occurring when either Durabolin or Deca-Durabolin is used.

Tausk: I am afraid I shall have to end this discussion now. Thank you again, Dr Hortling. I shall now call on Dr Dardenne from Bonn (Germany) to present his paper on “The Therapeutic Applications of Anabolic Steroids in Ophthalmology.”