SEX HORMONES AND MAMMARY CANCER

EXPERIENCE WITH DURABOLIN

BY

J. TH. VAN DER WERFF, M.D.

Radiotherapist, St. Canisius-Ziekenhuis, Nijmegen, Holland

Whilst the effect of hormones on the growth of cancer cells in general is still completely unknown, some relationship between sex hormones and cancer of the breast seems highly probable—a relationship that clearly is exceedingly complex. This is at once evident from the various ways in which a patient suffering from mammary cancer may react to sex hormone therapy. Ira T. Nathanson (1949) said: "The point which comes to my mind is that we may have two people of the same age, with the same tumour histologically, with the same physiologic characteristics, with the same mode of spread, who, to all intents and purposes, are metabolically identical; we give them hormones of the same kind, from the same bottle, on the same day; but one patient goes on to death in a short period of time and the other patient has a nice regression and goes on for a year and a half or two years before death."

The fact that of two mammary carcinomas of the same histological structure the one metastasizes in an entirely different way from the other suggests the existence of different kinds of breast cancer. The above-quoted statement concerning the experience that in spite of similar structure and metastases a different reaction to hormone therapy may occur shows that apparently there are various differences in the nature of these carcinomas which so far we have been unable to distinguish clearly by other means.

Statistics on the incidence of breast cancer in various age groups all show a kind of maximum in the climacteric, followed by a minimum and then a renewed increase. Pirquet (1930) inferred from this that there are two kinds of cancers—genital cancers and age cancers. I have recently (van der Werff, 1956) come to a somewhat different conclusion—that is, that two groups of breast cancer exist side by side: (1) oestrogen-dependent cancers which are stimulated by ovarian activity and can develop only in the reproductive period; and (2) age cancers which are independent of this ovarian activity and the disposition for which increases regularly with age (Fig. 1). This hypothesis explains why

FIG. 1.—Total chance of contracting mammary cancer, being the sum of the chances of age cancer and oestrogen cancer.

in some of the patients in the reproductive period oestrogen therapy results in a rapid exacerbation. In the menopause this seems to be not so, and sometimes oestrogens even have a favourable therapeutic effect.

As regards the androgens, they seldom seem to cause a rapid exacerbation, but have mostly either a clearly favourable, though merely palliative,

effect or none at all. The favourable response is seen mainly after administration of the most commonly used androgen, testosterone propionate, to patients with bone metastases.

Consequently, whereas it may be said of oestrogens that, according to the nature of the cancer, they have a positive, a negative, or no immediate effect on the growth of the tumour, it is far less clear whether androgens in certain cases can have a direct inhibitory effect on tumour growth or whether there is an indirect inhibition by means of the protein- and calcium-sparing action of these hormones, connected with stimulation of the general defence reaction.

However, in recent years it has become clear that, after prolonged administration and even in cases which originally showed a favourable response, androgens also in the end may stimulate tumour growth. This escapes observation because the impression is gained that the preparation has ceased to have effect.

Conversion of Steroids

In fact, according to recent research, the body is capable of gradually and to an increased extent converting certain androgens into oestrogens. This has long been suspected, not only from the similarity in structure of the oestrogenic and androgenic steroids but also from the fact that androgen therapy produced an increase in oestrogen excretion. While at first one might think of another process in which the production of oestrogens could be the result of stimulation by the administered androgens, recently more direct evidence has been obtained of a biological conversion of C19 steroids into C18 steroids by making use of radioactive ^{14}C . For example, incubation of human ovarian tissue and testicular tissue from stallions with testosterone-4- ^{14}C resulted in the formation of oestradiol-17 β - ^{14}C . Intravenous administration of the same labelled androgen to a pregnant mare gave rise to excretion of oestrone- ^{14}C . Finally the direct conversion of Δ^4 -androstene, 3,17-dione- ^{14}C into oestrogenic hormone could be demonstrated, for example, in the ovary, placenta, and adrenal (Meyer, 1955; Dorfman, 1956). It is clear, therefore, that for prolonged administration a steroid is needed which does not show this conversion and yet possesses the favourable properties of the androgens used for the treatment of mammary carcinoma. As already stated, it is not really known in precisely what way the androgen can favourably influence the carcinoma, but if we consider testosterone propionate we can say that the following properties are useful: (1) a pronounced protein-sparing effect; (2) an inhibitory effect on the decalcification process caused by the bone metastases and as a result a reduction in calcium excretion; and (3) an analgesic effect due to the action mentioned under (2). On the other hand, testosterone propionate has certain less desirable properties, the principal one being the virilizing action which becomes manifest in deepening of the voice and in beard growth.

Properties of Durabolin

Apparently the new compound, norandrostenolone phenylpropionate ("durabolin") compares favourably as regards all these properties with testosterone propionate, the first but until now the most important hormone for use in mammary carcinoma (Overbeek and de Visser, 1957). In the first place it seems that conversion in the body into oestrogen is not so easy or is perhaps even impossible, so that there is a possibility that far more prolonged administration is necessary (Meyer, 1955). In addition it has an anabolic effect 12 times more powerful than testosterone propionate, and the calcium excretion in patients with bone metastases can be greatly reduced after administration, while the virilizing effect is far less pronounced. The duration of action is long, so that weekly injections of 25 mg. are sufficient. The preparation is well tolerated, and patients who show a favourable response often begin to feel much better, acquire a good appetite, and look well. Although apparently conversion into oestrogen cannot be the cause, it has

unfortunately been found that in the case of durabolin the action wears off. From a certain moment the responsive patients also are seen to go slowly downhill and finally succumb.

Now, it is a significant fact that hormone therapy is almost exclusively instituted at an advanced stage, when the usual therapeutic measures have been exhausted and the patients show recurrences or generalized metastases, in which cases total recovery is no longer possible. It is feasible, therefore, that hormone therapy might have a curative effect if surgical and radiological treatments are immediately combined with the hormone therapy; but, on the other hand, in that case it will be very difficult to prove that this hormone therapy has been the decisive factor in the complete recovery. Without hormone therapy approximately one-third of the patients treated for cancer of the breast recover. A follow-up of a very large number treated in this way might produce the required evidence only after many years.

Results with Durabolin

The following results were obtained with durabolin in patients suffering from breast cancer. This group included 13 patients with such marked generalized metastases that recovery could not be expected. Eight of these have meanwhile died. In eight other patients the metastases were not yet very pronounced but other conditions made the prognosis very bad, and durabolin was administered to improve this. All are still alive.

In practically all 21 patients considerable improvement in the general condition was observed during weekly administration of 25 mg. of durabolin. This became manifest in alleviation of pain which was sometimes very severe as a result of bone metastases, in a good appetite which led to a considerable weight-gain, and in a general sense of well-being. This satisfactory condition, however, is often in complete contrast to the radiological findings. Although occasionally some slight calcification in bone metastases is observed, this is usually not clearly marked, and, in spite of a seemingly good general condition, the bones prove to be in a deplorable state.

In contrast to testosterone propionate, the durabolin is well tolerated for many months and the unpleasant symptoms of virilization occur only sporadically. The most striking of these is the inability to sing. Van Dommelen (1956) noticed that the administration of a single large dose of durabolin gave rise to such a severe calcium retention in the bones that there was a grave risk of hypocalcaemia and tetany. This was not so in any of the 21 patients, though the blood calcium usually fell slightly. In a number of cases the alkaline phosphatase was determined regularly. Here also varying reactions were found. In responsive cases in which this level was raised it fell fairly soon and continued to vary around a value which often was still too high. In one patient durabolin had no effect and the alkaline phosphatase continued to rise. When finally ethinyl-oestradiol ("lynoral") was given, this level fell critically. The case is discussed below. This patient belonged to the group of 13 of whom it was known beforehand that they could not be saved and of whom eight have died. Some of them, however, showed a dramatic improvement which, though of a temporary nature, was quite unexpected. Two of these cases are discussed in detail.

Case 1

A woman aged 43 had an operation in June, 1953, for carcinoma of the left breast and post-operative irradiation. In November she complained of "rheumatism" and stayed in bed for two months. Her doctor then treated her with testosterone phenylpropionate, and in March, 1954, she felt well and had gained 10 kg. in weight. However, gradually "shooting pains" began to occur again, and on January 1, 1955, having already given radiotherapy to the patient, I was called in for consultation and found her in a deplorable condition. She was suffering excruciating pains as a result

of generalized bone metastases and vomited after administration of morphine or other potent analgesics. The vomiting could be stopped immediately by injections of chlorpromazine. The pain could then be relieved with analgesics and the patient could again take food, after which the general condition improved. This improvement continued for a considerable time, but in July she was again in a hopeless condition. There were widespread metastases throughout the skeletal system.

In August durabolin therapy was instituted, first 25 mg. in a fortnight, then 25 mg. weekly, and still later 50 mg. a week. In September she was already feeling much better. The pain had gone and morphine was no longer needed. There was only a certain feeling of stiffness in the back, which was not surprising considering that the skeletal system was riddled with metastases. The alkaline phosphatase level fell from 39 King-Armstrong units in September, 1955,

FIG. 2.—Case 1. Alkaline phosphatase during treatment with durabolin.

to 19 in January, 1956, and then remained at that value. An increase in the durabolin dosage was of no avail (Fig. 2). In March, 1956, the pain suddenly became very severe again, and her condition gradually deteriorated. While about Christmas the patient had been so well that she could travel by train and stay with her relatives, she was now confined to bed, began to decline slowly, and died on July 21, 1956.

In the last few months durabolin was no longer tolerated. Virilization symptoms caused by durabolin were present only in a very slight degree.

Case 2

A woman aged 41 noticed a lump in the right breast in January, 1955, but did not go to the doctor until March, when there was also a lump in the axilla. The condition was complicated by a three-months pregnancy. She had an immediate operation, followed by irradiation, but in July there were supraclavicular nodules on the other side. Premature birth was induced and a healthy child was born.

On August 5, five days after parturition, large masses of nodules were observed in the neck. The neck was very painful, owing to a metastasis in C 2. There were also skin metastases around the vulva. Radiotherapy was given to the neck. Early in September the neck was still very painful but the nodules had disappeared. Unfortunately a tumour could now be felt in the left breast. Durabolin therapy was instituted, 25 mg. weekly. By the end of September the general condition had greatly improved. Only the tumour in the left breast was still present, but it had not grown larger. Mobility of the neck was much better. On October 11 her general condition was very good and the tumour in the left breast stationary.

Her general condition continued to be good. She could again do light housework and even ride her bicycle. She

FIG. 3.—Case 2. Alkaline phosphatase during treatment with durabolin.

was troubled only by a repeatedly recurring erysipelas, which could be easily suppressed with sulphonamides and penicillin. In May, 1956, she was looking very well indeed and felt well. The tumour in the left breast was still present, but was smaller and mobile. An ablation now took place, which healed without difficulty. All this time the patient was given durabolin, one dose of 25 mg. a week. The alkaline phosphatase level, which in September, 1955, was 20 K.A. units, had fallen, and in December, 1956, it was normal (Fig. 3). Unfortunately in January, 1957, her condition began to worsen and ascites developed. Durabolin began to lose its effect, and in late February it seemed as if the end was near. In connexion with an article by Goldsborough (1957) a course of chorionic gonadotrophin treatment was given (500 units three times a week). It has been reported that the patient is beginning to improve once more. She was still alive in April, 1957.

Case 3

This case, referred to above, shows that sometimes durabolin has no effect at all.

In April, 1953, a woman aged 42 felt a strand with three small lumps in the right axilla. When

FIG. 4.—Case 3. Alkaline phosphatase during treatment with durabolin and ethinyloestradiol.

in the course of that year the nodules grew larger she went to see her doctor, and after a biopsy specimen had been taken she had an operation. She had never felt anything in her breast. Post-operative radiotherapy was given and she remained in good condition till July, 1955, when she began to complain of pain in her back and lack of appetite. An x-ray picture showed a shadow in the right lung. The blood sugar was 50–94 mg./100 ml. In the evenings the temperature was subfebrile. After a few weeks' rest in bed her condition had slightly improved, but the subfebrile temperature remained.

Durabolin therapy was now instituted—first 25 mg. every fortnight, later every week. As a result the patient began to look better, but the pain in the back did not diminish. In January, 1956, this pain had increased. In an x-ray film the shadow in the right lung had gone, but there were now clear metastases in the ninth and tenth ribs. The temperature had gone up to 38.5° C. No metastases were observed in the vertebral column. An increase of the durabolin dosage to 50 mg. weekly produced no results.

As regards the alkaline phosphatase level, this had shown a continuous increase ever since October, 1955, till it reached nearly 60 K.A. units in March, 1956. In addition to the durabolin, 0.05 mg. of ethinyloestradiol was now given daily. It is remarkable that the alkaline phosphatase then fell to 17 K.A. units (Fig. 4). However, the pain in the back remained and the patient's condition deteriorated rapidly. Skin metastases began to develop also, and she died in May, 1956.

Comment

The three cases described here, and also the other 10 with marked metastases, show that in such cases we cannot expect a cure with durabolin, but, with the exception of a

single case, mentioned above, durabolin temporarily had an excellent effect. In one case calcification was observed in some of the metastases, as is sometimes seen after administration of testosterone propionate. Virilization symptoms were practically absent, and in no case did they bring inconvenience. Whether it is possible by means of durabolin to suppress metastases right at the beginning is, as already stated, obviously very hard to prove.

All eight patients who had no marked metastases but who gave cause for anxiety—for example, because the carcinoma was present during pregnancy or because they complained of vague and varying "rheumatic" pains—showed an excellent response and at the time of writing were free from cancer symptoms. All things considered, durabolin may justifiably be regarded as a valuable aid in the struggle against mammary carcinoma and as a preparation with clear advantages over testosterone propionate, the palliative value of which is established.

Summary

After a discussion on the effect of certain hormones used so far in the treatment of mammary carcinoma, including the new preparation durabolin (norandrostenedione phenylpropionate), some clinical results obtained with this preparation are reported.

It has been found that durabolin is usually a powerful and long-acting palliative which, owing to its very slight virilizing action, is a real asset in this treatment.

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ANTIBIOTICS IN ACUTE TONSILLITIS AND ACUTE OTITIS MEDIA

BY

JOHN FRY, M.D., F.R.C.S.

General Practitioner, Beckenham, Kent

Antibiotics are absolutely necessary in the treatment of serious bacterial infections. It is questionable, however, whether these expensive and potentially dangerous drugs are really necessary to treat all the much more frequent infections of the respiratory tract that abound in general practice. When and how should antibiotics be used for these common and relatively minor infections? Opinions differ greatly on the needs and indications, but apart from "opinions" there have been no planned studies into the matter.

This paper is an attempt to assess in a general practice the proportions of patients suffering from two readily definable and very common respiratory infections—namely, acute tonsillitis and acute otitis media—who required antibiotics in order to achieve satisfactory results, and at the same time the proportions who recovered equally well on non-specific treatment.

Methods

In carrying out this investigation the patients' interests were always of the first importance and no risk was taken or sacrifice made for the sake of the experiment. In any case of doubt the specific antibiotics were used, but where possible the aims were to withhold the antibiotics for 24 to 48 hours unless there were certain definite indications.