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MAMMARY CARCINOMA - RESPONSE TO IMPLANTATION OF MALE HORMONE AND PROGESTERONE

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A high percentage of certain strains of mice die from cancer of the breast and some women seem to have an inherited susceptibility to the disease. Apart from inherited susceptibility, one of the carcinogenic factors which may transform a normal cell into a cancerous one is said to be a surplus of oestrogenic substances in the body. It appeared, therefore, worth while to try to counteract the female hormone by male hormone.

Lascaud and Andervont (1939) and Murlin (1939), and Nathan and Andervont (1939) have published papers on the same subject, but they never used the implantation method—they made injections with male hormone. Sometimes they injected the mice at a very early age before they had litters (between the 1st and 21st day of life), and none of them treated the mice after the age of 4–5 months. If a mouse is treated with male hormone soon after birth there is a risk that the mammary gland will be arrested from development, in big doses causes an atrophy of the mammary gland as well as of the ovaries, and the suppression of the ovarian function may also be secondary to pituitary inhibition. No details of the different glands can be described in this paper, but the results of a long-continued action of testosterone on these glands are well known.

All the observers mentioned that testosterone protects from cancer of the breast a high percentage of mice I used in my experiments. Murlin influenced the growth and metastasis of the transplantable Brown-Pearce epithelioma by urinary androgens and considerably reduced the severity and mortality, especially when the injections were begun before the inoculation of the tumour. The workers quoted tried to counteract inherited susceptibility to cancer by injecting male hormone, and succeeded to some extent where they injected the mice at a very early age. But they undoubtedly altered the constitution of a female mouse if they injected the male hormone so early, and at the end of the course there was only a rudimentary mammary gland, or a gland which had never properly developed. It is not surprising therefore that these mice did not develop cancer of the breast, since the oestrogenic factor could not be formed while the ovaries remained atrophic; and these mice were never wholly female.

In the following experiments I used the implantation method. In one experiment some of the controls were treated with oestrogenic hormone in the tissues. It is perhaps worth comparing the results in strains of mice with a very high familial incidence of breast cancer and those obtained in women suffering from breast cancer who had a high familial incidence of the disease. Unfortunately the number of animals and patients who were treated and observed over several years was small. The animal experiments took place between February, 1939, and September, 1940. The war prevented me from breeding further generations of mice. It was also difficult to keep track of the patients over a sufficiently long period. Many of the treated patients left London before my observations were concluded, and only a small number could therefore be used for the purpose of this inquiry.

MOUSE EXPERIMENTS

Mice of Strong A strain were used. They show a very high incidence of breast cancer, and according to Bittner (1939) up to 88% die from breast cancer when they are eleven months old and have had several litters. I had at my disposal 354 mice born in the laboratory, but only 65 were bred and used either for implantation or as controls. Of these 65 only 22 remained for investigation over a period of thirteen to sixteen months; 43 died from other diseases or failed to have three litters. Of these 22 remaining mice 10 nos. 1–10) had testosterone propionate implanted and 12 nos. 11–22) were controls. Each of them had three litters, the 10 treated mice having 165 offspring altogether, and the controls to die. Mouse no. 20 died at 10 months of intercurrent disease. The 10 implanted mice died from cancer. Mouse no. 4 had no cancer when it died from an intercurrent disease at fourteen months. It was found that none of the mice which lived for more than fifteen or sixteen months died from cancer. All the mice of this strain which had not cancer by the age of twelve or thirteen months died from other causes, the age at death being between sixteen and eighteen months. Altogether 5 of the treated mice and 2 of the controls survived; 4 of the treated mice and 9 of the controls died of cancer; 1 treated mouse and 1 control died from other causes.

If we compare the 5 mice which did not develop cancer after the implantation with the 4 mice which did so, in spite of implantation, we find that 3 of the former had received implants before the age of six months, whereas all the latter received implants at six months or even later. The younger animals more implants have been made; thus the young mice received 7 implants. The fewer the implants the more limited the chance of protection. In some of the mice which developed cancer fresh implants were made even after the first appearance of the growth, but no beneficial effect could then be observed. Histological examination of the tumours revealed no difference in the treated and control cancerous mice.

I made no implantations until the mice had lived three litters, when forced orca had produced no carcinogenic substances without interruption for at least the first four and a half months of their lives. Thus not only was the hereditary factor acting but a surplus of oestrogenic substances has also stimulated the breast. Of the 4 mice which were implanted before the first half of their precancerous life was over, 3 appeared to be protected from cancer for fifteen months and more; whereas of 6 mice implanted nearer to the date when breast cancer in this strain usually appeared, 4 were not protected.

CLINICAL TRIALS IN WOMEN

The mamma is an organ in which there is a high familial incidence of cancer, often restricted to the immediate female relatives of the woman suffering from breast cancer, as the statistical investigations of Wassinck (1936) in Holland and of Weale in Norway have shown. I

<p>| TREATED MICE | CONTROL MICE |
|-----|-----|-----|-----|
| (Testosterone propionate 7–8 mg. in each implant) | (Testosterone propionate 7–8 mg. in each implant) |</p>
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traced back the history of my patients and found that in breast cancer ran in the family. All 6 patients had undergone operations for breast cancer and all had received X-ray treatment by experts. Male hormone was given to these patients to see whether when given over a long period it would inhibit severe metastases and influence recurrences. Naturally no prophylactic treatment could be applied before the first mammary cancer of this kind can be done in mice—membership of a family in which cancer runs is no indication for prophylactic treatment. Thus treatment could be started only when the normal mammary cells had already undergone some cancerous change. So in all there were no controls or symptomatic recurrence when male hormone was implanted; in the other 3 metastases were present at that time. Of the following cases 4 have already been published in part (Loeser 1939, 1940).

**Case 1.**—Married woman, aged 37; no children. Maternal aunt died from breast tumour. Radical operation in Johnesburg in June, 1939, after X-ray treatment. Recurrence at right clavicle in February, 1937. Histological examination revealed carcinoma. I performed curettage in April, 1937, because of uterine haemorrhage: hyperplasia of the endometrium. During May—September, 1939, breast testosterone propionate, 1500 mg., injected; resulting in amenorrhoea. In December, 1939, testosterone propionate, 600 mg., was injected. Symptoms of masculinisation appeared—enlargement of clitoris, hoarse voice, increased sexual urge, increased hair, gain in weight. These symptoms faded in June, 1938. In March, 1939, September, 1939, and March, 1940, testosterone propionate, 600 mg., was implanted again with the same result. In November, 1940, the patient was free from symptoms or signs of cancer.

**Case 2.**—Married woman, aged 42; two healthy children, one miscarriage. Paternal uncle died from cancer; grandmother died from breast tumour. Radical removal of breast performed September, 1935, after X-ray treatment. Recurrence in cicatrix on the left breast, March, 1936. Second radical operation in January, 1936; histological examination confirmed carcinoma. Curettage performed because of uterine haemorrhages; hyperplastic endometrium found. Between April, 1937, and January, 1958, testosterone propionate, 700 mg., injected; between October, 1939 to March, 1939, testosterone propionate, 600 mg., injected. In November, 1939, and June, 1940, implanations of testosterone propionate, 600 mg., were made. Signs of masculinisation followed as in case 1. In October, 1940, there were no signs or symptoms of cancer recurrence.

**Case 3.**—Spinster, aged 41. Mother died from breast cancer 18 months before. Radical operation on patient’s right breast in Budapest in 1936, after three courses of X-ray treatment. Supraclavicular recurrence in 1938, treated by X rays. In June, 1938, patient consulted me because of pruritus vaginalis; she had no recurrence of breast cancer. Between June and October, 1938, testosterone propionate, 700 mg., injected. In January, 1939, testosterone propionate, 500 mg., implanted; implantation repeated in June, 1939. Masculinisation as in the other cases. In December, 1940, there were no signs or symptoms of cancer.

**Case 4.**—Married woman, aged 60; two children. One sister had breast cancer. For the past eight years patient had been treated with radium for carcinoma of the breast. Multiple recurrences were treated by excision. Metastases on both sides, supraclavicular and mediastinal. Diffuse infiltration in right axilla. I experimented with X rays around the nipple. The radiologist called in recommended morphine for pain; on account of the disseminated carcinoma no other treatment was carried out. From July to October, 1939, testosterone propionate, 1500 mg., was injected. The temporary result was a superficial swelling around the right nipple, accompanied by considerable reduction of the ulcer, softening of the hard infiltration in the armpit, and superficial swelling and pigmentation of the healthy breast. Striking for these was an increase in appetite, and a general improvement in health; the pain along the right arm lessened considerably; the patient felt very well, walked about and looked after her household, whereas previously she had been confined to bed. The improvement lasted only four months, and a new implantation could not be performed owing to lack of material. The patient’s weight dropped again and further decline could not be checked.

**Case 5.**—Married woman, aged 45 years; no children. Sister had breast cancer and a male hormone 18 years ago, was suffering from cancer of the testis and had recently been operated on. Radical operation for cancer of the breast on the right side 1937, followed by much X-ray treatment in the next year. She had two recurrences in the operation scar and one in the axilla, which recurred in July, 1940. In November, 1939, testosterone, 1500 mg., was implanted. At first patient showed similar striking symptoms of improvement to those in case 4, but there was no change in the consistency or size of the recurrent tumour in the axilla, though there was no enlargement. X-ray treatment was again tried and this little tumour. Now recurrence in the armpit and left breast in April, 1940. As the patient had undergone temporary masculinisation after the implantation of testosterone, a trial was made of progesterone. In July, 1940, was implanted and daily doses of progestron, 40 mg., by mouth were given up to a total of 2800 mg. Menstruation stopped. No result was obtained; metastases in the liver with ascites was diagnosed.

**Case 6.**—Married woman, aged 38; no children. Paternal grandmother died from breast cancer. Two years ago operation was performed followed by X-ray treatment because of breast cancer. She had metastases in the mediatinum, with hoarseness. Supraclavicular glands involved on both sides. Radio- logist refused further X-ray treatment. Progesteron, 400 mg., was implanted and daily doses of progesteron, 40 mg., taken by mouth. There was no change in her condition. She had amenorrhoea for approximately a year, and after the implantation amenorrhoea continued. No improvement, further decline and death in November, 1940. The total amount of progesteron taken was 2400 mg.

Cases 1, 2 and 3 had one common feature: soon after radical operation and X-ray treatment they all developed recurrences; when treatment with male hormone was begun these were not present, for they had been either excised or had disappeared after X-ray treatment. Clinically these patients were free from any sign of cancer when the injections or implantations of male hormone were begun. But when they had received an average of 20 injections soon after operation they remained free from recurrences and metastases for 3-4 years (cases 1 and 2) and 2½ years (case 3) after the hormone treatment. It is now nearly five years since the operations were performed on all these patients and they are still in good health. These patients will have to be observed for several more years before any final judgment can be reached, and it will be necessary to continue hormone treatment from time to time. Even then it will be difficult to assume that masculinisation is responsible for the good result and the postponement of recurrences.

**Cases 4, 5 and 6.** All had metastases at the time when hormone treatment was begun. Cautiously and carefully under implantation of hormone treatment for the last two or three months, but the cancer itself remained unaltered and their decline could not be averted.

**DISCUSSION.**

There is a wide difference between inherited breast cancer in mice and carcinomas of the breast in women. Virgin or castrated female mice of the high incidence of breast cancer seldom suffer from cancer of the breast. Virgin or unmarried women acquire breast cancer more often than married women who have had children (Peller 1940). In my experiments the mice as well as the women showed a marked susceptibility to androgens of breast cancer. This susceptibility was further enhanced in the mice by oestrogenic substances developed in response to forced breeding as a result of which the mammary gland was exposed for a longer period of time to hormonal irritation. The same cannot be said of the patients; 4 of them had never had a child, and there is no reason to assume that their mammary glands had been exposed to any irritation by oestrogenic substances. Whether they produce any of these substances in their tissues cannot be said. But the antagonist of oestrogens was introduced into their circulation, and it is my impression that it was not the antagonist action alone but the alteration in the patient's condition—the masculinisation—which had an effect. The crescendo of masculinisation coincided with improvement in their condition; the diminuendo with progress of the disease.
Progestosterone can also be regarded as antagonistic to the follicular hormone. In my cases no effect of progestosterone on the cancer cells was observed. Progestosterone acts quicker when given by mouth than when implanted, and as it was only applied in hopeless cases no definite conclusions should be drawn; but it might be worth trying it in still more massive doses in cases which—like my cases 1, 2 and 3—are free from cancer at the time of treatment.

Incomplete as this series is, I hope it may encourage others to try out the idea and perhaps to implant testosterone or progesterone in cases of breast cancer at the time when the radical operation is performed. It may be implanted in the tissues of the operated breast whether postoperative X-ray treatment is given or not, and the implant should be repeated as soon as the signs of masculinization disappear. The effect of testosterone is always temporary, and may be compared with a temporary period of convalescence. The implant is therefore like a temporary stayconn on every tissue of the cancerous body instead of locally. I suggest that testosterone propionate, 700 mg., should be injected over two months. I have called this the hormone atrophy dose (H.A.D.) for the endometrium, since it tempers the tendency of the endometrium to atrophy (Losser 1940). It is better to implant testosterone propionate, 500 mg., than to inject 700 mg., since the implant has a more lasting effect.

**SUMMARY**

On the assumption that excess of estrogenic substance is a factor in producing cancer of the breast, an attempt was made to counteract this effect by implanting male hormone.

In mice of a strain showing a very high incidence of breast cancer testosterone propionate was implanted subcutaneously in 10 every three to five weeks while 12 acted as controls. Implantation was not begun until the mice had had three litters. In the treated group 4 and in the controls group 2 died of cancer.

In 6 women with a family history of breast cancer who had had their breasts amputated for carcinoma, testosterone propionate or progesterone or both were repeatedly implanted and in 2 progesteral was also given in the form of capsules of progesterone, and though 2 of these improved temporarily in general health, the progress of the cancer was not checked. In 3 no recurrences or metastases were present at the time of implantation, and none has appeared in the subsequent follow-up.

It is suggested that male hormone should be implanted in the operation site when the breast is removed for carcinoma, and implantation should be repeated after the healing process has occurred.

I wish to thank Prof. J. B. S. Haldane for allowing me to work in the Department of Biometry at University College, London; Dr. H. Grünberg and Dr. P. A. Gorin for giving me advice on breeding mice; Miss M. Watson my assistant; and the Schering Corporation of New York and Organon Laboratories for supplying testosterone and progesterone tablets.

**REFERENCES**


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**Reviews of Books**

**Lipidoses : Diseases of the Cellular Lipid Metabolism**

*Steepheid T. Thannhauser, M.D., Ph.D., formerly professor of medicine, University Clinic, Freiburg; associate professor of medicine, Tafel College medical school, London: Humphrey Milford, Oxford University Press. Pp. 376. 30s.*

Most of our knowledge of this group of metabolic disorders has accumulated during the last twenty years, a period during which Professor Thannhauser has contributed to the solution of the cases of lipidoses, and the "Lipidoses" has been edited. The book will be of interest to both physicians and geneticists. It abounds in tables and figures and contains full records of the cases observed by the author. Appropriately enough, the section on cholestasis occupies most of the book; it embraces 12 primary types divided into 4 subtypes, the lactic acidosis and 2 other types. Gaucher's disease and Niemann-Pick's disease are fully considered in separate sections.

The author has no doubt that the primary lipidoses are manifestations of abnormal intracellular metabolism in the reticular and histiocytic cells of the organism, supporting this concept with convincing biochemical and experimental evidence. He regards an imbalance of intracellular processes as the fundamental disturbance. The research worker will reap a rich harvest from the 1076 references which are conveniently arranged at the end of each section.

**Parenthood : Design or Accident?**


This excellent little book on birth control and related problems needs no introduction either to the medical profession or to the public. In this edition recent research work on spermicides is included; the description of the technique of well-established and desirable methods has been rewritten in the light of modern experience; dangerous, ineffective, emergency and experimental methods are fully discussed; and is the safe period. It would be difficult to find a more lucid and concise description, or a more helpful evaluation, of this much publicized method of family limitation. The sections on the sociological, ethical and legal aspects of contraception remain materialy unchanged. The list of references includes lists of birth control clinics in the United Kingdom and of approved and reputable advertisements. There is also a short bibliography, glossary and index.

**Arthritis and Allied Conditions**


This is a large book but not too large, for arthritis and other conditions loosely termed rheumatic occupy a considerable part of medical practice here as well as in the United States. In fact, rheumatism is the result of much study (there are references to over two thousand original papers) into a small space. General practitioners, as well as physicians especially interested in chronic rheumatism, will find much to interest them and to use in their practice, though they will probably use the book more for reference than for light reading on dark evenings. The illustrations are good and more than in the first edition, while new chapters have been added and many old ones rewritten. Curiously, the paging of the sections of each chapter is given in the table of contents, not the paging of the papers. The index is full.

**Out of the Test Tube**


Few of us without special knowledge of the subject ever pause to consider the material benefits conferred by chemistry upon mankind. In his expanded and revised edition Dr. Holmes gives a vigorous account of what science is doing and will do for us. Our food, tools and clothing, our medicines, means of transport and weapons of war are all a few of the accepted accomplishments of modern life which are profoundly influenced by chemistry. It is depressing to reflect on how high explosive has been largely diverted from its proper purpose of quarrelling and rock and stone-eating slaves; or to realize that profit-making rather than philanthropy has been a prime motive of chemical research. But we shall change all that in the brave new world after the war.