MAMMARY CARCINOMA

RESPONSE TO IMPLANTATION OF MALE HORMONE AND PROGESTERONE

ALFRED A. LOESER, M.D. BERLIN, L.R.C.P.E.

(Department of Biometry, University College, London)

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 œstrogenic substances in the body. It appeared, therefore, worth while to try to counteract the female hormone by male hormone.

Lacassagne (1939), Raynaud (1939), Murlin (1939), and Nathanson 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 4–4½ months. If a mouse is treated with male hormone soon after birth there is a risk that the mammary gland will be prevented from developing. Male hormone 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 changes in 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 showed that testosterone protects from cancer of the breast a high percentage of mice of the strain I used in my experiments. Murlin influenced the growth and metastasis of the transplanted Brown-Pearce epithelioma by urinary androgens and considerably reduced severe metastasis 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 œstrogenic 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 order to maintain a permanent source of counteracting 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 83% 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. Out of these 65 mice, only 22 remained for investigation over a period of thirteen to sixteen months; 43 died from intercurrent disease or failed to have three litters.

Of the 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 189. Every three to five weeks 7–8 mg. of testosterone propionate was implanted subcutaneously in tablet form, being embedded in the subcutaneous fat of the back of mice nos. 1–10. After three or four weeks the small tablet was usually absorbed.

Of the 12 control mice 9 died from cancer of the breast (see table). They usually showed the first sign of cancer between the tenth and eleventh month and on an average it took a month from the beginning of the disease for them to die. Mouse no. 20 died at 10 months of intercurrent disease. Of the 10 implanted mice 4 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 who lived for more than fifteen or sixteen months died from cancer. All the mice of this strain which had no cancer by the age of twelve or thirteen months died from some other cause, 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.

RESULTS OF IMPLANTATION OF TESTOSTERONE PROPIONATE IN MEMBERS OF A STRAIN OF MICE SUSCEPTIBLE TO MAMMARY CANCER

TREATED MICE (Testosterone propionate 7–8 mg. in each implant)				CONTROL MICE	
No.	Age at first implant (months)	No. of implant	Result	No.	Result
1	4½	7	Living, 15 mths; no cancer	11	Died cancer, 12 mths.
2	5½	7	Living, 15 mths; no cancer	12	Died cancer, 13 mths.
3	6	7	Died cancer, 14 mths	13	Died cancer, 14 mths.
4	5½	7	Died, 14 mths; no cancer	14	Died cancer, 13 mths.
5	8	3	Died cancer, 10 mths.	15	Died cancer, 12 mths.
6	8	5	Living, 16 mths; no cancer	16	Living, 16 mths; no cancer
7	5½	4	Living, 15 mths; no cancer	17	Died cancer, 13 mths.
8	8½	5	Died cancer, 12 mths.	18	Died cancer, 12 mths.
9	8	4	Living, 15 mths; no cancer.	19	Living, 15 mths; no cancer.
10	9	4	Died cancer, 13 mths.	20	Died, 10 mths; no cancer
				21	Died cancer, 12 mths.
				22	Died cancer, 12 mths.

If we compare the 5 mice who did not develop cancer after the implantation with the 4 mice who 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 a mouse the more implants can be made; thus the young mice received 7 implants. The fewer the implants the more limited the chance of protection. In some of the mice who 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 had three litters, when forced breeding had produced œstrogenic 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 œstrogenic substances had 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 Wassink (1936) in Holland and of Waaler in Norway have shown. I

traced back the history of my patients and found that in 6 breast cancer ran in the family. All 6 patients had undergone operations for breast cancer and after the operation had had 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 metastasis and influence recurrences. Naturally no prophylactic treatment could be applied before the first appearance of cancer, as 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 cancerous change. In 3 of the 6 there were no signs or symptoms of 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 Johannesburg in June, 1936, after X-ray treatment. Recurrence above right clavicle in February, 1937. Histological examination revealed carcinoma. I performed curettage in April, 1937, because of uterine hæmorrhage; hyperproliferation of the endometrium found. During May–September, 1937, patient had testosterone propionate, 1500 mg., injected; resulting in amenorrhœa. In December, 1937, testosterone propionate, 600 mg., was injected. Symptoms of masculinisation appeared—enlargement of clitoris, hoarse voice, increased sexual urge, increased growth of 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. The voice remains hoarse.

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; excision. Second recurrence in armpit, October, 1936; histological examination confirmed carcinoma. Curettage performed because of uterine hæmorrhages; hypertrophic endometrium found. Between April, 1937, and January, 1938, testosterone propionate, 700 mg., injected. December, 1938 to March, 1939, testosterone propionate, 600 mg., injected. In November, 1939, and June, 1940, implantations 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 tumour, illness lasting four years. 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 vulvæ. At that time 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 with a suppurating ulcer the size of half a crown around the nipple. The radiologist called in recommended morphine for pain; on account of the disseminated carcinosis no other treatment was carried out. From July to October, 1939, testosterone propionate, 1850 mg. was implanted. 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 features were an increase in weight by 5 lb. and obviously improved 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. 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 had breast cancer, and a nephew at the age of 18 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 a fresh recurrence in the axilla in July, 1939. From August to 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 recurring tumour in the axilla, though it showed no enlargement; X-ray treatment dissipated this little tumour. New 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, progesterone, 300 mg., was implanted and daily doses of progesteral, 40 mg., by mouth were given up to a total of 2800 mg. Menstruation stopped. No result was obtained; metastasis in the liver with ascites was diagnosed.

CASE 6.—Married woman, aged 28; no children. Paternal aunt died from breast tumour. Two years ago operation was performed followed by X-ray treatment because of breast cancer. She had metastases in the mediastinum, with hoarseness. Supraclavicular glands involved on both sides. Radiologist refused further X-ray treatment. Progesterone, 400 mg., implanted in August, 1940, and for two months daily doses of progesteral, 40 mg., taken by mouth. There was no change in her condition. She had amenorrhœa for approximately a year, and after the implantation amenorrhœa continued. No improvement, further decline and death in November, 1940. The total amount of progesteral 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 either been 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 although they had shown recurrences 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 the male hormone 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. Cases 4 and 5 improved strikingly under implantation treatment for the first 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 carcinoma of the breast in women. Virgin or castrated female mice of strains with 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 an inherited susceptibility to breast cancer. This susceptibility was further enhanced in the mice by œstrogenic substances developed in response to forced breeding as a result of which the mammary gland was exposed without interruption 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 œstrogenic substances. Whether they produced abnormally high amounts of these substances in their tissues cannot be said. But the antagonist of œstrogens was introduced into their circulation, and it is my impression that it was not the antagonistic action alone but the alteration in the patient's constitution—the masculinisation—which had an effect. The crescendo of masculinisation coincided with improvement in their condition; the diminuendo with progress of the disease.

Progesterone can also be regarded as antagonistic to the follicular hormone. In my cases no effect of progesterone on the cancer cells was observed. Progesterone 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 masculinisation disappear. The effect of testosterone is always temporary, and may be compared with a temporary sterilisation, which in contrast to X rays acts 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 temporarily sterilises any healthy woman and makes the endometrium atrophic (Loeser 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 œstrogenic 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 9 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 by mouth. In 3, recurrences were present at the time of implantation, 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 five years.

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 when signs of masculinisation disappear.

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Reviews of Books

Lipidoses : Diseases of the Cellular Lipid Metabolism

SIEGFRIED T. THANNHAUSER, M.D., Ph.D., formerly professor of medicine, University Clinic, Freiburg; associate professor of medicine, Tufts College medical school. London: Humphrey Milford, Oxford University Press. Pp. 370. 30*s*.

MOST of our knowledge of this group of metabolic disorders has accumulated during the last twenty years, a period covered by Professor Thannhauser's contribution of the section on lipoid diseases to the "Oxford Loose-Leaf Medicine." The publication in book form of this monograph by one who has contributed so much to this particular branch of medicine will be welcomed by all interested in the lipoidoses. The volume, which is well edited by Prof. H. A. Christian of Harvard, is abundantly illustrated and embodies full records of cases observed by the author. Appropriately enough, the section on xanthomatosis occupies most of the book; it embraces 12 primary types divided into hypercholesteræmic and normocholesteræmic groups, and 8 other types. Gaucher's disease and Niemann-Pick's disease are fully considered in separate sections.

The author has no doubt that the primary lipoidoses 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 lipoidases 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?

(4th ed.) MICHAEL FIELDING. London: Williams and Norgate. Pp. 259. 2*s*. 6*d*.

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; so also is the safe period. It would be difficult to find a more lucid and concise description, or a more helpful evaluation, of this much publicised method of family limitation. The sections on the sociological, ethical and legal aspects of contraception remain materially unchanged. The appendices include lists of birth-control clinics in the United Kingdom and of approved and reputable appliances and chemicals. There is also a short bibliography, glossary and index.

Arthritis and Allied Conditions

(2nd ed.) BERNARD I. COMROE, M.D., F.A.C.P. London: Henry Kimpton. Pp. 878. 42*s*.

THIS is a large book but not too large, for arthritis and various conditions loosely termed rheumatic occupy a considerable part of medical practice here as well as in Philadelphia. In fact Dr. Comroe often compresses 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 help them in their choice of therapy, though they will probably use the book more for reference than for light reading on dark evenings. The illustrations are good and more profuse 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 chapters themselves; but the index is full.

Out of the Test Tube

(3rd ed.) HARRY N. HOLMES, Ph.D. New York: Emerson Books Inc. Pp. 305. $3.

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 the chemist, working in divers spheres, has done, is doing and will do for us. Our food, tools and clothing, our medicines, means of transport and weapons of war are only a few of the accepted accompaniments 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 quarrying rock and so liberating slave-labour; or to realise 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.