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THE EFFECT OF THE ALTERATION IN THE ENDOCRINE STATUS
ON BREAST CANCER.

Introduction - A Review of the Literature.

It is the purpose of this thesis to show how the problem of the physiological action of the secretions of the gonads has been gradually elucidated, and how, as a result of earlier work, alterations in the normal hormone balance of the body have come to be utilised in the treatment of carcinoma of the breast.

The relationship between the breast and the ovary was first mentioned by Sir Astley Cooper as long ago as 1829, but the knowledge first came to be applied clinically at the end of the nineteenth century.

Schinzinger, at the Surgical Congress in Germany in 1889, first suggested bilateral oophorectomy as an auxiliary method of treatment for carcinoma of the breast. He was of the opinion that the disease was more rapidly fatal in younger women, and that castration, by hastening the advent of old age, would slow down the rate of growth of the tumour.

Beatson, independently, suggested the same treatment in 1896, and he also prescribed thyroid to augment the effect. He thought the disease was caused by ovarian dysfunction, and he noted some remarkable/

remarkable results - shrinkage of the primary tumour and the disappearance of skin nodules and enlarged lymph glands. In a published series of cases in 1911, he came to the conclusion that the procedure was only justified in women over 40 who were still menstruating.

Others published groups of cases; Boyd (1900) reported 19 improved out of 54; Thomson (1902) 29 improved out of 80; and Lett (1905) 41.3% improved, when patients of over 50 were excluded from the series.

With the advent of X-rays, it was thought that the same effect, namely the elimination of ovarian function could be brought about as effectively and with less danger to the patient by ovarian irradiation, and in 1909, 1922 and 1926, Fouveau de Courmelles reported a series of cases in which he noted a more rapid regression of the primary tumour when X-ray treatment of the primary tumour was combined with irradiation of the ovaries.

Ahlbom (1930) also reported rapid improvement in cases similarly treated, but he found no effect on the survival rate. Dresser, Martin and Smith in 1936, and Taylor in 1939, have all reported cases showing temporary arrest or calcification of bone metastases. Farrow (1944) found that one-third of pre-menopausal cases received some benefit. He also admitted, however, that local X-ray treatment to metastases/

metastases had, in many cases, been combined with ovarian irradiation. This, of course, makes estimation of results more difficult, but other, non-irradiated metastases were also found to regress.

The essential point emerging from all this work was that elimination of ovarian function was of temporary value in women of the pre-menopausal age group suffering from breast cancer.

Additional information concerning the role of sex hormones in cancer of the breast has been obtained from experimental studies in animals, especially in mice.

Geneticists observed many years ago that certain inbred strains of mice showed a high incidence of spontaneous mammary adenocarcinomata in females. Further inbreeding and selection has resulted in the production of several inbred strains in which mammary tumours have appeared for many successive generations (Slye 1927). These have been called mice of "high cancer strain". Among mice of other strains mammary tumours appear rarely or not at all. These are known as mice of "low cancer strain".

Lathrop/

Lathrop and Loeb (1916), Loeb (1919), and Cori (1927) showed that early spaying of female mice reduced the incidence of naturally occurring mammary carcinoma. Ovariectomy of mice at the age of 3 to 5 months largely inhibited the occurrence of mammary tumours. The incidence of such tumours was greater in mice ovariectomised when 5 to 7 months old and was not altered in mice ovariectomised at later ages.

The part played by the ovary in producing breast cancer was also shown by the work of Murray (1928). He transplanted ovaries of female mice into the abdomens of their brothers. The incidence of carcinoma of the breast in the male mice rose from 0% to 7%, while the incidence in the female fell.

It was natural that experiments should be carried out in an attempt to induce breast cancer in mice by the administration of one of the oestrogens, but the earlier preparations were not concentrated, and it was not until 1932 that Lacassagne first reported a carcinogenic effect of the oestrogens on mammary glands.

He used a strain in which multiparous female mice frequently developed mammary cancer, but in which/

which male mice never did. He showed that breast tumours, resembling those occurring naturally in the females, could be induced in the male mice by weekly injections of 0.03 mgm. of crystalline oestrone benzoate in oily solution. Female mice, similarly treated, developed a higher incidence of breast cancer at an earlier age.

The administration of oestrogens of widely different chemical structures such as oestradiol, equilin, equilenin and their benzoates and propionates, stilboestrol and triphenylchloroethylene, were found to effect similar mammary changes (Lacassagne 1936⁽¹⁾ and 1938; Robson and Bonser 1938).

There appeared to be two possible explanations for these findings. The oestrogen may have been the direct cause of the malignant growth or it may merely have initiated mammary proliferation so that more cells were available to undergo malignant transformation under the influence of some other factor. The problem was further investigated by Lacassagne (1933). He injected mice from a low cancer strain with folliculin. These mice showed a higher incidence of tumours after the injections. But in strains where/

where mammary tumours rarely appeared spontaneously, no tumour appeared after the injection of an oestrogenic substance, showing that, in mice, the oestrus-producing hormone must act only in combination with some other factors in mammary carcinogenesis.

Such factors were indeed found. Susceptibility to breast cancer in mice was found to be a transmissible factor, the mother being found to be relatively more important than the father in the transmission (Little 1933; Murray and Little 1936; Bittner and Little 1937).

This particular factor was called the genic transmissible factor. Bittner (1940) demonstrated the presence of a further factor which was transmitted to suckling mice in the mother's milk. This he called the non-genic transmissible factor. This factor is not limited to the first milk, but is present throughout the period of lactation. The active influence conveying susceptibility can be transferred at the age of 4 weeks by oral administration of milk from a mother from a high cancer strain. It can also be transmitted by implanted tissue - liver, spleen and thymus.

However, some mice were found to be resistant to/

to the non-genic transmissible factor (Murray 1941) The nature of the factor is unknown, but it seems to be essential for the development of breast cancer under the action of one of the oestrogens in mice.

From a study of these results, it is obvious that the oestrogenic group of compounds are no more than a contributing factor in the initiation of mammary neoplasia. This conclusion is supported by two further observations.

The age at which treatment was begun, and the length of time during which the mammae were subjected to the effects of these hormones seemed to be important. Burns and Schenken (1940), using the C₃H strain of mice and injecting 100 i.u. of oestradiol benzoate a week subcutaneously, found that the maximum effect was produced when treatment was begun at the age of 2 weeks and continued until 16 weeks.

It was also reported by Gardner in 1941 that the highest incidence of carcinoma was induced by the doses of oestrogens which were most favourable for mammary growth. There was found to be an optimum dosage by which maximum development of the breast/

breast was attained. Within limits, the larger the amounts of oestrogen administered and the greater the inherited tendency to cancer, the earlier the mammary tumours appeared. (Suntzeff, Kirtz, Blumenthal and Loeb - 1941).

These facts might seem to indicate that the oestrogens may have little direct effect upon mammary carcinogenesis in mice. There is, however, some evidence indicating a direct carcinogenic effect. Mammary growth occurs in animals with functional pituitary glands when oestrogens are injected. In the presence of some other factor or agent and an oestrogen, localised proliferative or pre-cancerous nodules of breast tissue appear. The development of mammary adenocarcinoma in and among the localised nodules can occur subsequently in the absence of oestrogens. Oestrogens may, therefore, contribute to the pre-malignant phase of tissue change or to the environment in which these changes occur (Gardner 1944).

The action of others of the steroid hormones has also been investigated. Nathanson and Andervont (1939) carried out work using testosterone propionate in mice. They found that testosterone when given to uniparous mice of 4 months of age or/

or less would prevent the development of tumours provided there were none present when treatment was begun. It was assumed that tumours which had developed had been microscopic when treatment commenced and had not been influenced in growth rate.

Smaller amounts of testosterone - 1 mgm. weekly - reduced the incidence of tumours in virgin mice when the injections were started early in life, but did not alter the appearance of the tumours in multiparous animals (Jones 1941). Jones also concluded that injections of testosterone did not inhibit the growth of mammary gland tumours once they reached macroscopic size.

Loeser (1941) reported that the implantation of pellets of testosterone propionate into multiparous mice of the strong A strain reduced the mortality from spontaneous cancer from 75% in the controls to 40% in the treated animals.

Progesterone, when administered with an oestrogen, causes no difference in the incidence of mammary tumours compared with the result with an oestrogen alone (Lacassagne - 1937). The doses of progesterone were perhaps too small.

The hormones of the adrenal cortex were also investigated/

investigated. Desoxycortisosterone acetate 2 to 4 mgm. a week, induced mammary growth in male mice (van Heuverswyn, Folley and Gardner 1939). One milligramme or less per week did not lead to mammary cancer in male mice of the C₃H strain or alter the incidence of tumours in female mice (Shimkin and Grady 1941).

The close relationship between the ovaries and the adrenals was brought out, however, by Fekete, Woolley and Little in 1941. They found that in mice, the vagina, uterus and mammae recovered from an early castration atrophy. In mice, where the ovaries were removed on the day after birth, they found a nodular hypoplasia of the adrenal cortex 14 to 23 months later, and concluded that when the endocrine balance is upset, compensatory changes take place in other parts of the system.

It has been found also that the effects of the administration of an oestrogen depend on the species of animal and on the strain or breed used e.g. pituitary tumours have been reported in mice (Zondek 1936; Cramer and Horning 1936), lymphoid tumours and leukaemia in other strains of mice (Lacassagne 1936⁽²⁾) and Lipschutz and Iglesias (1938) were able to produce fibromyomata of the uterus in guinea/

as the incidence of carcinomas in the normal guinea-pigs.

The effects on women were investigated by Zondek (1940 and 1947). He states that following the administration of very large doses of oestradiol to women over a long time, there develops a papillary erosion of the cervix and an abundance of cervical glands and glandular hyperplasia of the uterine mucosa. Corpus luteum formation was prevented so that negligible quantities of progesterone were produced and the output of the follicle stimulating hormone (F.S.H.) of the anterior pituitary was also decreased. Amenorrhoea of varying duration was produced in pre-menopausal women.

The number of cases of human cancer reported as following or appearing in time after the administration of any of the oestrogens is limited (Auchincloss and Haagensen 1940; Allaben and Owen 1939; Parsons and McCall 1941). Abramson and Warshawsky (1948) quote the case of a man receiving 1097 mgm. of diethylstilboestrol in 489 days for prostatic carcinoma, who developed bilateral mammary carcinomata.

It is difficult to be clear about the carcinogenic properties of any substance in human beings/

beings, as the incidence of carcinoma in the normal population is sufficiently high to make many coincidences inevitable.

There are only a limited number of observations of the effects of oestradiol and related substances on established cancer in animals. Haddow (1938) studied it in mice with mammary carcinoma, but no inhibition of growth was seen.

The growth of transplanted sarcomata was not appreciably changed by the injection of oestrin (Bischoff and Maxwell - 1936). Doses of Dimenformon (oestradiol benzoate), large enough to induce dwarfism failed to prevent the growth of benzpyrene-induced tumours (Zondek 1937). One transplanted mammary adenocarcinoma showed inhibited growth and secretory activity when oestradiol benzoate was injected (Eisen 1941).

As was stated at the beginning, the first work done on the treatment of human breast carcinoma by interfering with the hormone balance of the body was the removal of normal ovarian function either by surgical extirpation of the ovaries or the destruction of the active secreting cells by X-irradiation. This was started on a purely theoretical/

theoretical basis and being found to have an value has been continued in certain cases.

In the late 1930's however, as a result of all the experimental work mentioned, the problem was placed on a more scientific basis, in spite of certain discrepancies and contradictory evidence.

It was natural, in view of the possibility of the induction of cancer of the breast with one of the oestrogens and the apparent inhibitory effect of androgens, the latter should be tried in the treatment of the disease. Early reports were somewhat contradictory, but it was clear that significant alterations in the disease might occur after such therapy.

Ulrich (1939) first described treatment with testosterone propionate, but the doses he gave were too small to produce castration. Two patients however showed improvement.

Loeser (1938; 1940; 1941) also using testosterone propionate reported relief of bone pain and recalcification of osteolytic bone metastases, but discovered no improvement in the primary tumour, lymph glands or visceral metastases.

Farrow & Woodard (1942) on the other hand found that in some cases with bony metastases treated with/

with testosterone there was an increased activity of tumour cells as evidenced by clinical and X-ray findings and accompanied by a rise in calcium excretion.

Farrow (1944) concluded that though the patient might experience a temporary feeling of well-being and relief from pain, those effects were inconstant and transient and excess of the hormone might cause acceleration of the disease.

Treatment of series of cases with testosterone has, however, continued up to the present day.

Herrmann, Adair and Woodard (1947)⁽³⁾ found symptomatic improvement in patients of all ages with bone metastases. Doses were of the order of 120 to 200 mgm. bi-weekly. They started investigations into the blood chemistry, reporting a rise in serum alkaline phosphatase in 8 out of 17 cases, which, in the absence of liver disease, they took to mean bone growth and attempt at bone regeneration. They thought that, as a result of the endocrine imbalance produced following initiation of treatment, some mechanism involving the pituitary and suprarenals stimulated osteoblastic activity and alkaline phosphatase production. Counting as a normal value of serum alkaline phosphatase 3 to 5 units per 100 cc., they found values/

values up to 15 units % under treatment with testosterone. In advanced cases they also found a high initial value of serum calcium - as high as 17 mgm. %, and that this came back slowly to normal under androgen therapy, the calcium theoretically being deposited in the bones.

The changes in blood calcium and phosphorus are, however, not well understood.

Alkaline phosphatase is present where there is osteoblastic activity, whether reparative in osteolytic metastases or in actively growing osteoblastic metastases, or where both processes are proceeding simultaneously. Therefore a rise in alkaline phosphatase may mean more osteoblastic metastases rather than repair of osteolytic metastases (Cutler and Schlemenson - 1948).

The same authors also reported that testosterone increases retention of sodium and potassium, and pointed out that the gain in weight which occurs generally under treatment may not necessarily mean a favourable response, but merely water retention. Seventy-two hours after stopping testosterone, there occurs a diuresis and loss of weight (Thorn and Engel 1938).

Syiven and Hallberg (1948) came to the conclusion/

conclusion that with doses of testosterone propionate of the order of 50 mgm. a day for 2 - 3 weeks, and a maintenance dose of 150 mgm. a week, the main effects were a striking improvement in general health and a relief from pain, both being only temporary and disappearing as soon as the androgen was stopped. The effect was concluded to be non-specific and thought to depend on the physiological action of testosterone in increasing protein metabolism. They were of the opinion that androgens did not influence the growth rate of established mammary cancer.

Kaae (1949), using doses of 100 to 200 mgm. bi-weekly, found that in younger patients some regression in the primary tumour and in the soft tissue metastases occurred, but that in elderly patients the main beneficial effects were the improvement in general health and the relief of pain.

Very little has been reported on the effect of the administration of progesterone to cases of advanced breast cancer. Loeser (1941) reported a trial of this hormone in cases of advanced breast carcinoma. No effect was noted and the disease appeared to follow its usual course.

The/

The administration of the oestrogens on the other hand, to women with advanced cancer of the breast would seem to be entirely illogical, but the fact remains that they are capable of producing striking alterations in the course of the disease.

Zondek (1940) states that he was the first to use oestradiol in a case of recurrent breast cancer. This he did in 1935. His reasons for adopting this method are very interesting, in that they are still worthy of consideration even to-day, fifteen years later.

In the first place he thought that, as large doses of the oestrogens caused inhibition of the output of the gonadotrophic hormone of the anterior pituitary, this would bring about a cessation of ovarian function - in other words, a hormonal castration. This would in effect be the same treatment that earlier workers had used by surgical or radiotherapeutic means. In the second place, he thought that, as large doses of oestrogenic hormone was supposed to produce dwarfism by inhibiting the release of the growth hormone from the anterior pituitary, this might also cause an inhibition of tumour growth. This was supported by the fact that it had been reported/

reported that in hypophysectomised rats a Jensen carcinoma failed to grow.

On these hypotheses therefore, he gave 0.6 gm. of oestradiol benzoate daily for 60 days to a woman with recurrent breast carcinoma, but there was no response, and his work does not seem to have been followed up immediately.

Interest in the problem of the hormonal control of malignant disease especially cancer originating in the sex organs, received another impetus as a result of the work of Huggins on the treatment of carcinoma of the prostate by castration and stilboestrol.

Huggins' clinical work was based on a long series of ingenious animal experiments. He demonstrated that the administration of androgens stimulated prostatic activity and increased the flow of prostatic fluid. It was shown that the administration of oestrogens stopped the production of prostatic fluid. Androgens caused hypoplasia of the epithelial cells of the prostate, metaplasia even becoming so marked as to simulate cancer. Oestrogens caused a return to normal. Huggins also showed that after surgical castration, prostatic secretion stopped.

He felt then that as malignant prostatic tumour/

tumour was frequently merely an overgrowth of adult epithelial cells, castration, by removing the main source of natural androgens, would have a restraining effect on the growth. Men also excrete oestrogenic hormones in their urine, the source of these being taken as the adrenals. After castration, therefore, the output of oestrogens should remain constant, thus bringing about a shift in the oestrogen-androgen ratio towards a higher oestrogen and lower androgen level. Obviously the administration of oestrogens per se would bring about a similar sort of shift.

The control of the response to such treatment was made by the estimation of serum acid and alkaline phosphatase levels. Acid phosphatase is present in adult prostatic epithelial cells. It is also present in the hypoplastic prostate, in cancer of the prostate and in metastases from the latter. (Gutman, Sproul & Gutman 1936). The level of acid phosphatase indicates the activity of the cancer. Alkaline phosphatase is produced in excess by bone as a defence mechanism. Where there are bony metastases, the activity of the bone defence is indicated by the amount of alkaline phosphatase in the blood.

In 1941, Huggins and Hodges published their original report on cases of carcinoma of the prostate/

prostate. They noted that castration or injections of stilboestrol or oestradiol benzoate produced a fall in acid phosphatase and a rise followed by a fall in alkaline phosphatase. This was accompanied by a remarkable improvement in the patient's general condition. Testosterone propionate injections induced a sharp rise in acid phosphatase.

Actually it was found later (Dean, Woodard & Twombly - 1944) that from the point of view of excretion of hormones, castration and the administration of oestrogens apparently do not produce their effect in the same way. Castration causes a decrease in oestrogen excretion, while the excretion of androgens, as measured colorimetrically as 17 - ketosteroids by the Callow-Zimmerman test, tends to remain the same or rise slightly. Actually the figures they give do not show a convincing rise. On the other hand they found that stilboestrol causes a decrease in excretion of 17- ketosteroids and, of course, a rise in oestrogen excretion.

Various groups of workers began to take a more active interest in the hormone treatment of otherwise hopeless cases of breast cancer, but apart from Zondek none tried the effect of an oestrogen. Even the work of Huggins, though stimulating, does not lead logically to oestrogen treatment in women.

The/

The first mention in the literature of work of this nature was the symposium published in June 1944 in the Proceedings of the Royal Society of Medicine. The work appears to have been started independently in various centres as a result of the growing interest in the relationship between malignant disease and sex hormones. The fact that castration and male hormone had been tried for many years with only limited success prompted a search for further measures, and a fuller investigation of the subject obviously included a trial of the effect of the oestrogens. Ellis et alia (1944) carried this out.

The drugs used in this series of cases were stilboestrol and triphenylchloroethylene. All were agreed that a useful effect was seen in a small proportion of women, but that the best results were seen in patients of 60 and over. There were no excessive side reactions apart from occasional nausea and vomiting. Doses used were of the order of 2 to 15 mgm. of stilboestrol a day and 1.5 gm. twice a day of triphenylchloroethylene. Most benefit was obtained in local recurrences and lymph glands, but one writer (Paterson) noted relief of pain in bone metastases. Some thought there was a correlation between pathology and response, but this was not a general finding. Paterson thought that/

that more cellular tumours were more responsive and concluded that because these tumours were more vascular, the drugs had easier access.

Another approach to the subject was made by Haddow et alia who published his views in September 1944. He had found that in an investigation into the mechanism of action of tumour-producing compounds, many carcinogenic hydrocarbons possessed the property of retarding the growth of tissues, both normal and malignant. He considered that the correlation between carcinogenicity and growth-inhibitory action might be of aetiological significance, tumour production being envisaged as a cellular adaptation to a protracted period of growth repression. He next drew attention to the relationship of these compounds to the synthetic oestrogens. Some carcinogenic hydrocarbons possess slight oestrogenic activity, and in certain cases an interesting relationship on chemical grounds, e.g. in animal experiments with triphenylchloroethylene (which can be likened to 9-phenylphenanthrene with one ring disrupted), it seemed that growth-inhibitory activity may still be shown by compounds which depart from the polycyclic structure and possess only a resemblance in their carbon skeleton. Contrariwise some oestrogens are carcinogenic as evidenced/

evidenced by the experiments of Lacassagne and others.

It was therefore judged to be reasonable to undertake the clinical trial of synthetic oestrogens in advanced human cancer which was beyond the aid of surgery or X-rays - with particular reference to tumours arising from such tissues as are reactive to the physiological stimuli of these compounds e.g. the breast.

Treatment of these cases started in late 1942. Forty cases of carcinoma of the breast and 33 cases of other types of malignant disease were treated with triphenylchloroethylene. A proportion showed a temporary regression of some of the metastases from breast carcinoma. One metastasis might regress while another advanced. Only 1 showed a prolonged arrest. Of other types of malignant disease only 1 bladder and 1 prostate showed any response.

One patient out of 4 with breast cancer treated with triphenylmethylethylene showed a temporary response and 4 out of 14 showed a slight response to stilboestrol.

Farrow (1944) also apparently working independently reported on 3 patients with skeletal metastases/

metastases treated with oestrone. Unfortunately from the point of view of assessment, the patient's had previously had large doses of testosterone propionate. Oestrone was given parenterally and the doses were relatively small, 2 to 4 mgm. He found that both testosterone and oestrone caused a hypercalcaemia, which he took to be due to increased activity of the metastatic tumour and acceleration of bone destruction. He concluded therefore, at that time, that both male hormone and the oestrogens accelerated the rate of growth and were contra-indicated.

Nathanson (1946), admitting that he was influenced by workers in this country (Haddow et alia and Ellis et alia 1944) reported a series of cases treated with stilboestrol. He found that in older women there was a temporary benefit in some as evidenced by epithelialisation of ulcers. Hermann, Adair and Woodard (1947)⁽¹⁹⁴²⁾, also influenced by the earlier work in Britain, tried the effect of another oestrogen - ethinyl oestradiol. Dosages used were 0.5 to 0.7 mgm. a day. Of 17 women, 7 showed a favourable response, 5 having soft tissue metastases and 2 pulmonary metastases. The patients who responded were all over 60.

No changes were detected in serum calcium, phosphorus/

phosphorus or alkaline phosphatase. Vaginal smears showed that all had developed an oestrous reaction.

These authors were of the opinion that the effect might be produced through the anterior pituitary.

The position with regard to the administration of androgens and oestrogens in mammary cancer was summed up in 1947 by the Sub-Committee of the Therapeutics Trials Committee of the Council on Pharmacology and Chemistry in the United States. They emphasized first that hormone therapy was only palliative, and that only very advanced cases should be selected for this form of treatment.

They concluded that androgens offered the promise of relief in cases of bone metastases regardless of the age of the patient, the dose being of the order of 100 mgm. of testosterone propionate tri-weekly. Benefit was seldom to be expected in the primary tumour or in soft tissue metastases. Relief became obvious in from 2 to 3 weeks, but the duration was variable. They came to no conclusion as to the mode of action, but suggested that it might be by means of medical castration i.e. inhibition of the gonadotrophic hormone/

hormone of the anterior pituitary.

The criteria for the selection of patients for treatment by one of the oestrogens were different. They thought that women over 60 with soft tissue metastases were likely to do best, and the dose level recommended was of the order of 5 to 20 mgm. a day of diethyl stilboestrol. The evidence for improvement in bone metastases was not conclusive. They advised that the oestrogens should not be given until at least 5 years after the menopause.

Further work on the whole subject has been reported since 1947, and efforts are being made to discover the mode of action of these drugs.

Adair et alia (1949) reported a series of 105 female patients with either primary or recurrent inoperable mammary cancer treated with oestrogens and androgens.

Seventy were treated by intramuscular injection of testosterone propionate, 100 mgm. thrice weekly for a month or longer. 19% of 48 with skeletal metastases showed improvement, and 15% of 54 with extra-skeletal metastases also showed regression. Improvement lasted 2 to 11 months and longer, for some of the patients were still alive when the article was published. The most impressive feature again was the improvement in general health and/

and the relief from pain. Good responses were seen in women of all ages. Some were symptomatically improved, even although the disease was progressive. Oestrogenic substances (diethylstilboestrol, ethinyl oestradiol, oestrone sulphate and oestradiol benzoate) were given to 35 patients. Objective improvement occurred in 23% in extra-osseous metastases. No favourable effect was seen in osseous metastases.

With diethyl stilboestrol, which was given as 5 mgm. thrice daily up to a total dose of 210 to 1470 mgm., improvement, when it occurred, lasted 2 to 17 months. All the patients were 2 or more years past the menopause.

In the biochemical investigations they made, they found that in patients with bony metastases, 46% had elevation of serum alkaline phosphatase, and 23% had elevation of serum calcium before treatment. This is reasonable when one remembers that the first is an indication of the bone defence mechanism, and that in an osteolytic process, calcium from the bone may temporarily flood the circulation. 63% of patients with osseous metastases had an increase of serum alkaline phosphatase during the first three months of treatment and it fell after that. A fall occurred in serum calcium level after treatment was commenced. There/

There was no suspicious change in serum alkaline phosphatase levels in patients with extra-skeletal metastases.

56% of all patients treated with ethinyl oestradiol or testosterone propionate had a significant decrease in serum inorganic phosphorus.

Histological and histo-chemical investigations in those patients under treatment for subcutaneous lesions showed that in those showing a good response, degenerative changes were seen in the nucleus and cytoplasm of the cancer cells, and there was a fibroblastic proliferation and sclerosis of the connective tissue.

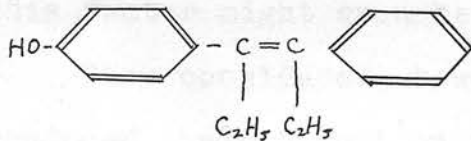
Haemoglobin levels increased under treatment with testosterone from 12.6 gm. to 15.9 gm. per 100 cc.

Cytological changes in enfoliating vaginal mucosa were seen in the direction of basophilia after androgen administration and acidophilia after oestrogen administration. In the stratified squamous epithelium of the cervix the cytoplasmic glycogen content either increased or remained constant in half the cases during androgen or oestrogen therapy.

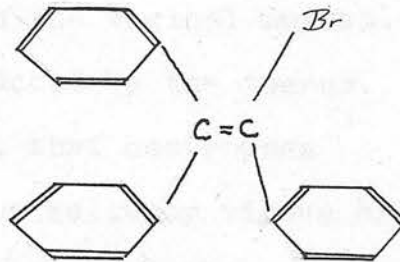
Further investigations were carried out by Walpole and Paterson (1949). Oestrogens were given to/

to 50 post-menopausal women with breast cancer and the results were compared on a quantitative basis with concomitant changes in the vaginal epithelium.

The drugs used were stilboestrol and dienoestrol, 5 mgm. four times a day and 1.2 mgm. a day, and M 2612, 300 to 600 mgm. a day. The formula of M 2612 is given and compared with that of stilboestrol.



Stilboestrol



M. 2612

An interesting method of clinical assessment was used, each individual metastasis being assessed and graded and the values added to give a mean clinical index. The vaginal response was graded according to the degree of keratinisation of the cells.

It was found that in some, isolated metastases responded while others advanced or new ones developed. In a proportion however, there was a good response in the disease as a whole. Clinical improvement was greatest in older patients and in those/

those receiving the larger doses of the hormones. Vaginal keratinisation was most pronounced in older women, but was not related to dosage.

In general there was a correlation between clinical improvement and vaginal epithelial reaction. Some patients seemed to be refractory to oestrogens. This suggested to these workers that in such patients there was some factor involved tending to prevent both an effect on the tumour and also the normal physiological effect on the vaginal mucosa. This factor might even be produced by the tumour.

They considered, however, that oestrogens produced their effect on tumour cells by virtue of their oestrogenic properties, because substances of different chemical structure were useful, the only apparent common factor being their oestrus-producing propensities. Also all the effects produced so far have been on tumours of sex organs such as breast and prostate.

With respect to carcinoma of the male breast, the reports are naturally rarer.

Leucutia (1946) and Nathanson (1947) both reported a beneficial effect following orchidectomy and Paterson (1944) noted regression of metastases following treatment with triphenylchloroethylene.

THE/

THE DEVELOPMENT OF HORMONE TREATMENT IN THE RADIO-
THERAPY DEPARTMENT ROYAL INFIRMARY EDINBURGH.

The development of hormone treatment for advanced carcinoma of the breast in cases seen in the Radiotherapy Department of the Royal Infirmary of Edinburgh roughly parallels the development which has been traced in the world at large.

In 1937-38 ovarian irradiation was first tried in pre-menopausal patients for the treatment of recurrences and metastases. Several of the cases in the pre-menopausal group showed a dramatic response - disappearance of soft tissue metastases and recalcification of osteolytic bone metastases. It was found, however, in the course of time that even the most dramatic of these responses was short-lived, and the patient's condition later deteriorated.

The causes of this failure were sought and it was thought that perhaps ovarian function recovered to some extent after irradiation. The dose given was small - about 700 to 800r - and normal tissues such as the ovarian stroma are not so easily put out of action by X-rays as rapidly dividing malignant cells. Function might be depressed for a few months and then return almost to normal. This is seen in women under 35 particularly in whom it is very difficult to bring about an artificial menopause./

menopause.

It was decided therefore in 1940 to treat some recurrent cases by bilateral oophorectomy supplemented by post-operative injections of testosterone propionate. In this way, all natural oestrogenic activity might be supposed to be inhibited. Only a small series was treated in this way, but as no dramatic successes were produced, it was concluded that as far as the elimination of ovarian function was concerned, oophorectomy was at least not superior to X-radiation and was more of an ordeal for the patient.

These methods so far were logical, agreeing with previous work, experimental and clinical, but it was obvious that a search had still to be made for further therapeutic agents. Further sex hormone treatment would only take the form of the apparently illogical course of the administration of one of the oestrogens. On this basis therefore stilboestrol dipropionate began to be used in late 1942. This formed part of the earliest work on this aspect of the subject, the first 37 cases forming the largest group to be reported in the symposium presented at the Proceedings of the Royal Society of Medicine in June 1944 (McWhirter).

Most of the patients received stilboestrol dipropionate, but oestradiol benzoate, dienoestrol and/

and triphenylchloroethylene were also tried.

To complete the investigation a small series was treated in 1944 with ethisterone, without any success however.

In 1949, ethinyl oestradiol began to be used as it was reputed to be more potent but less toxic, but it is too soon to evaluate these results.

The most outstanding factor emerging from the work with the oestrogens was that their value was limited to post-menopausal women. Therefore in an attempt to help younger women and those who had not responded to other measures, and also to determine the value of testosterone propionate alone, a further series treated with male hormone was begun in July 1949. As these results have been very disappointing and good responses the exception, it is felt that it is not too soon to include their assessment. They will, therefore, be included in the results which are now to be considered.

Cases under Consideration.

All the cases considered in this review were referred to the Radiotherapy Department from 1936 onwards suffering from carcinoma of the breast. Over 500 case records have been analysed and in recent years I have examined all such patients personally and have supervised their treatment.

The majority were treated in the first place
by/

by simple mastectomy of the affected breast followed by X-ray therapy to the chest wall and axilla of the same side. A few were treated on a palliative basis by X-ray therapy alone. Many had subsequent X-ray therapy to isolated metastases.

Treatment of a hormonal nature was instituted where:-

- (a) The primary tumour was inoperable when first seen and the patient's general condition was so poor as to make radiotherapy inadvisable.
- (b) Local recurrence had taken place in an area previously irradiated to full dosage.
- (c) There were widespread metastases - cutaneous, glandular, visceral or boney.

In the groups receiving ovarian irradiation, oophorectomy + testosterone, oestrogens or ethisterone, the series include cases where treatment was given in the years 1940-47 and the results are assessed up to 31.12.48.

In the last group receiving testosterone propionate alone in 1949 the results are assessed up to the end of January 1950.

In no case considered however, was the assessment of response to a hormone invalidated by any other form of treatment. In the majority receiving sex hormones, previous X-ray therapy had been/

been given three months or more before and the full effect had been observed. In the remainder, where palliative X-ray therapy was given to isolated metastases, the response to the drug was judged by the progress of the other metastases.

Over the years 1940-47, ovarian irradiation was frequently given combined with X-ray treatment to a single metastasis and was also given in 1946-47 prophylactically with the first X-ray treatment. All these cases have been excluded in assessing the value of ovarian irradiation. However, where such cases received hormones subsequently for recurrences or metastases they have been included in the general review with regard to their response to that drug. They have also been considered later as a separate group because as will be seen, there appears to be a difference in response.

Assessment of Results.

The results have been grouped so that the following information would be obtained:-

1. The type of response possible, and the percentage in which favourable responses occurred.
2. The relationship between response and age, especially with regard to the time of occurrence of the menopause, and to the type of treatment given.

3. The effect, if any, of the histological type of the tumour on response.
4. The differences, if any, in the response shown by metastases in different sites - skin, lymph glands, viscera and bone.
5. The optimum dosage desirable where a drug is given.
6. The symptoms associated with such treatment, and any contra-indications.

D. Adverse reactions Drugs Used.

Stilboestrol dipropionate, "Dimenformon" (oestradiol benzoate), dienoestrol, triphenylchlor-ethylene, "Ethisterone" (androhydroxyprogesterone) "Perandren" (testosterone propionate).

Grading of Response.

Responses were graded as follows:-

A. Good response.

1. Complete disappearance, even if only temporarily, of soft tissue metastases and/or
2. New bone formation as demonstrated radiologically in bony metastases and/or
3. Remarkable improvement in general health.

B./

B. Fair response.

1. Regression of soft tissue metastases, but not complete disappearance and/or
2. Some improvement in general health, relief of pain.

C. No response - steady progression of disease.

These three, A, B, and C, apply to all groups considered, but further subdivision was necessary where hormones were administered.

D. Adverse response - apparent acceleration of disease.

E. Response to withdrawal of drug.

F. Response uncertain. This comprises a miscellaneous group of patients most of whom were in the terminal stages when treatment by hormones was considered. They were not seen again in the Department, and there is no proof that all received the hormone treatment prescribed. Their numbers are mentioned in each group, but in calculating the percentage responses they have been omitted as, apart from the fact that many may not have received any hormone, those who did were probably given it too far on in the course of the disease to derive any benefit.

It will be noticed that only cases receiving hormone therapy have been considered. No comparison has been made with recurrent cases where the disease has been allowed to pursue its usual course.

This has seemed to me to be fair, because the value of this type of treatment has been judged by actual observed regression in clinical manifestations of the disease. Now in all, about 4,000 cases of breast cancer have been observed in the Radiotherapy Department since 1930 and in no case has actual regression of metastases been seen, although there are naturally occurring fluctuations in general health.

The survival rate has been mentioned in the groups of cases which will be considered, and although it does seem that life can be prolonged with hormone treatment, no attempt is made to claim success on this account alone.

Consideration/

Consideration of the Response to Ovarian Irradiation

The technique of treatment has varied slightly with the passage of time, but the aim was to deliver to the ovaries in a single treatment a dose of about 700r to 800r by means of an X-ray beam directed into the pelvic cavity from the anterior and posterior aspects. This was sufficient, in women who had not reached the menopause, to bring about a cessation of menstruation.

It was given to women of all ages however, to determine the effect on the post-menopausal patients as well.

Table I.

Total Number of Cases = 149

Graded according to Response

Response	Nos.	%
A - good	15	10.07
B - fair	17	11.41
C - none	117	78.52
	149	100%

Table II.

Average Age and Relation to the Menopause.

Response	Average Age (yrs)	Relation to Menopause.
A - good	43.13	All pre-menopausal but 1
B - fair	43.35	All pre-menopausal but 2
C - none	49.73	54 or 46.15% pre-menopausal

If pre-menopausal patients are considered as a separate group it is found that approximately 36% showed a response of some degree.

It will be seen from these tables that a small group experienced some benefit from ovarian irradiation, 10.07% becoming symptom free, and in many cases completely well clinically, and 11.41% having some relief. As a general rule, those who have not reached the menopause seem to have a better chance of showing a good response. The only one among the good responses who was not pre-menopausal was only 55. The time of occurrence of the menopause in this patient was unknown. Similarly, in those showing a fair response only two were post-menopausal, and their ages were 53 and 63.

However, not every pre-menopausal case responds well - 46.15% of those showing no response were in this category.

Table III/

Table III.
Relation of Response to Pathology.

Histological Type	A Good response		B Fair response		C No response	
	No.	%	No.	%	No.	%
Adenocarcinoma	-	-	1	5.88	18	15.41
Adenocarcinoma with scirrhous reaction	6	40.00	6	35.30	23	19.65
Anaplastic carcinoma	2	13.33	5	29.41	16	13.67
Anaplastic ca. with scirrhous reaction	4	26.67	3	17.65	22	18.80
Intraduct carcinoma	-	-	-	-	2	1.71
Paget's disease	-	-	-	-	1	0.85
Scirrhous ca. (only description given)	1	6.67	-	-	5	4.27
Ca. showing colloid degeneration	-	-	-	-	4	3.42
Ca. showing squamous metaplasia	-	-	-	-	2	1.71
Tumour described only as 'carcinoma'	-	-	-	-	2	1.71
No pathology available	2	13.33	2	11.76	22	18.80
Total	15	100%	17	100%	117	100%

The numbers in groups A and B (i.e. those showing some response) are small and this makes assessment difficult. The four most common types of tumour are represented however, viz. glandular and undifferentiated carcinomata both with and without a scirrhous reaction. It would seem therefore, that response cannot depend on histological type, and this will be seen again in the/

the groups of cases receiving hormones.

Type of Metastases showing a favourable Response.

It could not be said that one type of metastasis responded better than another. Glands and skin nodules disappeared or regressed in 21, osteolytic bone metastases showed new bone formation in 2, in 4 a pleural effusion disappeared, and in 4 it became less. One patient showed regression of orbital metastases and one of lung metastases.

Cases grouped according to Survival after Ovarian Irradiation.

Table IV.

Response	Survival in Months.
A - good	23.67
B - fair	18.29
C - none	8.89

Ovarian irradiation, when it produces a good response, also appears to have an effect in prolonging life. This has to be interpreted carefully because (a) there are many individual exceptions in the cases reviewed and (b) the natural course of the course of the disease is very variable.

The/

The difference between the average survival in A and in C is so great however, that even bearing these qualifying facts in mind, there seems no doubt that life is prolonged and that the treatment can have an arresting effect on the course of the disease.

Consideration of Cases treated by Surgical Cas-
tration and/or testosterone.

Total Cases = 9

In 4, bilateral oophorectomy followed by daily intramuscular injections of 25 mgm. perandren (testosterone propionate) was given as the first treatment in advanced inoperable cases. Three of these had bony metastases when first seen. The total dosage of testosterone given varied between 1125 and 2750 mgm.

Only one case showed any response - Case No. 19,207 Mrs. C.N. aet 40. Details of this case are as follows:-

When first seen the patient had a tumour involving the whole right breast. The tumour was fixed to the pectoral fascia and there were partially fixed glands in the right axilla. There were osteoplastic metastases in the lumbar spine.

A biopsy of the tumour was carried out and it proved to be a scirrhous adenocarcinoma.

The patient had not reached the menopause. A bilateral oophorectomy was carried out and treatment with perandren begun. The patient received 102 daily/

daily injections of 25 mgm. each. The primary tumour became smaller and the glands disappeared. No effect was noted on bony metastases.

Later a simple mastectomy was carried out followed by a palliative course of X-ray therapy. She was later given stilboestrol and then dienoestrol in an effort to control the spread of the bony metastases, but without any useful effect. She then had palliative X-ray therapy to the lumbar and dorsal spine.

She lived 37 months after the date of the bilateral oophorectomy.

In the remaining 5, castration and the administration of male hormone were tried in 3, castration alone in 1, and male hormone alone in one, for the treatment of recurrences and metastases in cases treated in the first place by a combination of surgery and radiotherapy.

Two had local recurrences in the chest wall only, one had bony metastases only and two had metastases in glands and bone.

Their average age was 49.0 yrs.

None showed any response.

Consideration of Cases where Treatment by Oestradiol benzoate or Stilboestrol dipropionate was prescribed irrespective of other hormone treatment given earlier or later.

Consideration of Cases where Treatment by Oestradiol benzoate or Stilboestrol dipropionate was prescribed irrespective of other hormone treatment given earlier or later.

Table V.

Total Cases = 279

Graded according to Response

Response	Total Nos.	Nos. with uncertain response "F" withdrawn.	% with "F" withdrawn
A - good	21	21	9.63%
B - fair	44	44	20.18%
C - none	123	123	56.43%
D - adverse	23	23	10.55%
E - withdrawal response	7	7	3.21%
F - uncertain	61	-	-
	279	218	100%

Only 4 patients received oestradiol benzoate and none showed any response.

There was only 1 male patient in this group. He was 36 years of age and became rapidly worse under treatment by Stilboestrol dipropionate.

Average/

Average Age and Relation to the Menopause of the Female Patients.

Table VI.

Response	Average Age (yrs.)	Relation to Menopause.	% who are pre-menopausal.
A - good	68.00	None were pre-menopausal	0 %
B - fair	63.66	5 " " " of which all but 1 had previous O.I. [⊗]	11.36%
C - none	56.85	28 were pre-menopausal of which all but 7 had previous O.I.	23.00%
D - adverse	51.30	11 were premenopausal of which all but 4 had previous O.I.	47.82%
E - withdrawal response	58.57	1 was pre-menopausal and had had O.I. 2 months before Stilboestrol	14.28%

⊗ = Ovarian Irradiation.

Several points emerge from a study of these tables:-

1. The percentage who show a response of some kind i.e. A + B + E or 33.02% is gratifying when one considers that all these patients are in a hopeless position, beyond the aid of surgery or radiotherapy. The good responses or 9.63% show, in most cases, complete clinical disappearance of the disease for varying periods of time.
2. It was interesting that some patients showed a response on stopping the treatment. They did not appear to become worse while receiving the hormone/

hormone, but any regression occurring took place one to two months after stopping. In no case was there more than a slight response. The effect may have been in the nature of a delayed response. In general these were younger women, but only one was pre-menopausal.

3. The relation to the time of occurrence of the menopause is significant. None of those who showed a good response was pre-menopausal and the youngest was 58. In the group showing only a fair response only 5 or 11.36% had not reached the menopause in the normal way. As stated 4 of these 5 had an artificial menopause induced by ovarian irradiation before commencing with stilboestrol. This was done because it had been noted that post-menopausal women responded better to stilboestrol. However the effect of ovarian irradiation on the response to the subsequent administration of stilboestrol is an interesting point which will be considered separately later.

In groups showing no response, or an adverse response the percentages in the pre-menopausal group were higher, 22.76% and 47.82% respectively.

Response in relation to Pathology.

Table VII/

Response in relation to Pathology.

Table VII

Histological Type	A good response		B fair response		C no response		D adverse response		E With - drawal response	
	No.	%	No.	%	No.	%	No.	%	No.	%
Adeno. Ca.	1	4.76	3	6.82	11	8.80	2	8.70	1	14.28
Adeno Ca. with scirrhous re- action	6	28.57	14	31.82	33	26.40	7	30.43	2	28.58
Anaplastic Ca.	4	19.05	4	9.09	14	11.20	3	13.04	2	28.58
do. with scirrhous reaction	5	23.81	8	18.18	21	16.80	5	21.74	1	14.28
Intraduct Ca.	-	-	-	-	3	2.40	-	-	-	-
Paget's dis- ease with intraduct Ca.	-	-	-	-	1	0.80	-	-	-	-
Scirrhous Ca. (only descrip- tion given)	-	-	-	-	2	1.60	-	-	-	-
Ca. showing colloid degen- eration	-	-	-	-	5	4.00	-	-	-	-
Ca. showing squamous meta- plasia.	-	-	-	-	2	1.60	1	4.35	-	-
No pathology available	5	23.81	15	34.09	33	26.40	5	21.74	1	14.28
Total	21	100%	44	100%	125	100%	23	100%	7	100%

N.B. Under Group C (no response) there are 125 tumours whereas the number of patients in this group was 123. One patient had two tumours in the same breast, one scirrhous and one colloid, and one patient had a tumour in each breast, and both were intraduct carcinomata.

It/

It is apparent that consideration of the pathology alone is not a safe criterion in deciding whether a case will respond to treatment by stilboestrol or oestradiol, nor can the explanation for the action of these hormones on malignant cells be based on histological type.

This is interesting because the position with regard to the histology and radiosensitivity of certain tumours is somewhat analagous e.g. meningiomata, where it has so far been impossible from histology alone to differentiate between the radiosensitive and the radio-insensitive. (McWhirter 1946).

Relation of Response to the Site of Metastases.

Each type of metastasis was graded as for its own response e.g. in a patient where the overall response was classified as "fair", but where glands regressed and bone metastases continued to advance in this table glands would come under the heading B or "fair response", and bone metastases under C or "no response".

Table VIII/

Relation of Response to the Site of Metastases.

Table VIII.

Site of malignant involvement.	A good response		B fair response		C no response		D adverse response		E With- drawal response	
	No.	%	No.	%	No.	%	No.	%	No.	%
Local recurrence or skin nodules	14	32.56	28	37.33	83	33.74	17	38.64	7	50.00
Glands	17	39.54	32	42.67	89	36.18	14	31.82	4	28.60
Bone	5	11.63	11	14.67	38	15.45	7	15.91	3	21.40
Lung	3	6.97	1	1.33	14	5.70	1	2.27	-	-
Pleura (as evidenced by effusion)	3	6.97	-	-	12	4.88	4	9.09	-	-
Abdomen	-	-	1	1.33	4	1.62	1	2.27	-	-
Brain	-	-	-	-	5	2.03	-	-	-	-
Orbit	1	2.33	2	2.67	1	0.40	-	-	-	-
Total	43	100%	75	100%	246	100%	44	100%	14	100%

On the whole there is no significant difference in the percentages of the different types of metastases showing response as compared with the percentages showing an adverse response or no response at all. Where the total numbers are small as in the less common sites of metastases and in the smaller response groups such as E and F, there is naturally more discrepancy in the figures and assessment of significance is difficult.

In general, in a patient showing a good response, there was improvement in all the kinds of metastases/

metastases present. Sometimes, however, one metastasis regressed while others continued to increase in size or new areas of involvement developed.

One very interesting point is the relatively large numbers of bone metastases which benefited, 11 having relief from pain and 5 actually showing new bone formation in osteolytic metastases as demonstrated radiologically. This is well illustrated in a case which will now be described in more detail.

Case No. 11,124 Mrs. E.B.

This patient originally had a radical excision of the right breast for carcinoma in 1928 when she was 43 years of age.

She kept well until October 1944 when she developed proptosis of the left eye. She was seen in the Radiotherapy Department for the first time on 24.5.45, when she was found to have metastases in the left orbit and enlarged glands in the left side of the neck. There was also diffuse involvement of ribs, skull and pelvis by metastases which were partly osteoplastic and partly osteolytic (see Plate I).

Stilboestrol dipropionate 5 mgms. b.i.d. was prescribed on 23.5.45. By 28.6.45 the proptosis had/



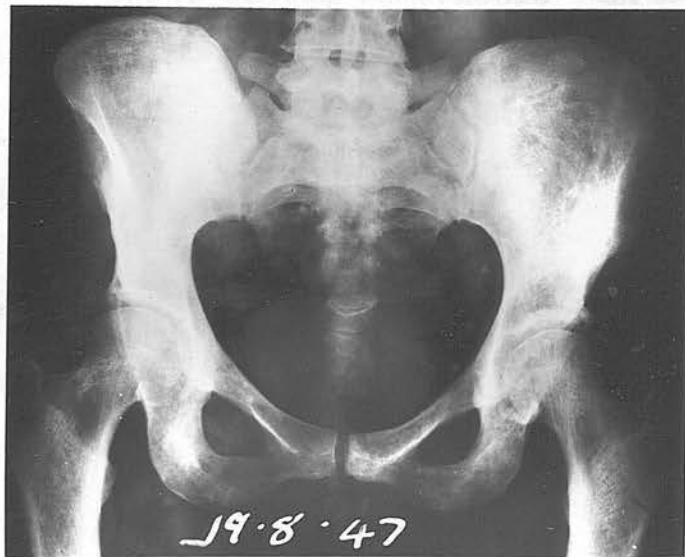
Mrs. E.B. Case No. 11,124

Plate I.



24.5.45 X-ray pelvis before administration of Stilboestrol. Diffuse involvement by metastases which are partially osteoplastic and partially osteolytic.

Plate II.



19.8.47 X-ray pelvis after treatment by Stilboestrol. Considerable new bone formation has taken place in the osteolytic areas and the trabeculation is restored almost to normal.

had almost gone and on 2.8.45 the glands were no longer palpable and the left eye appeared normal apart from slight ptosis of the upper lid.

On 19.8.47 an X-ray film of the pelvis and chest showed marked improvement in the bony metastases (see plate 2). By 28.2.46 no abnormality could be seen in a film of the skull.

She continued with stilboestrol dipropionate but was advised to take 5 mgm. b.i.d. on alternate months.

The breast condition remained well till the end of 1948 but unfortunately on 16.12.48 carcinoma of the fundus of the stomach was diagnosed. She went rapidly downhill and died on 27.8.49.

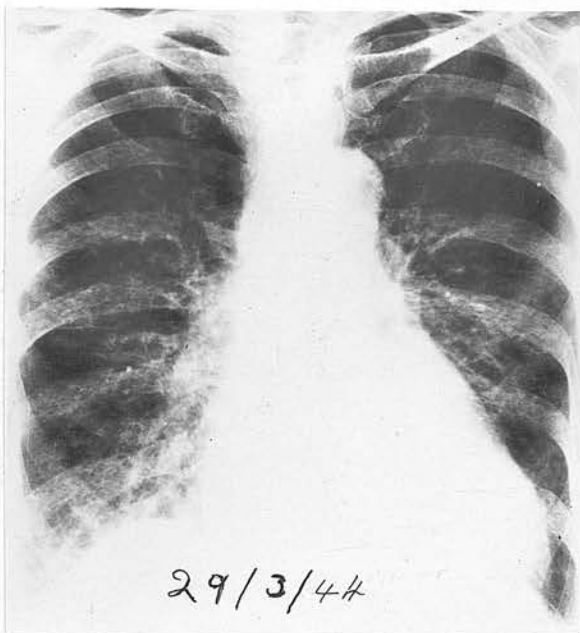
Several cases showed remarkable improvement in lung metastases. Two of these will be described.
Case No. 19,621 Mrs. C.D. aet 66.

The patient was first seen in the Department on 29.3.44 with an extensive carcinoma involving the whole of the left breast with an area of ulceration 7 x 4 cm. There were separate skin nodules, fixed glands in the left axilla and mobile glands in the left supraclavicular region and opposite right axilla. X-ray examination showed diffuse metastases in both lungs (see Plate 3).

She was started on stilboestrol dipropionate 5 mgm. b.i.d. on 30.3.44. Biopsy of the tumour carried out on 4.4.44 showed no peculiar feature of interest./

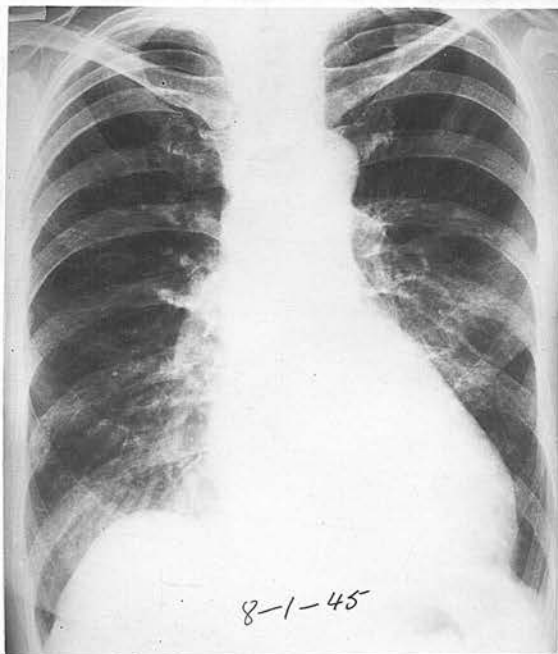
Mrs. C.D. Case No. 19,621

Plate 3



29.3.44 X-ray chest before administration of Stilboestrol. Diffuse metastatic involvement in both lung fields.

Plate 4



8.1.45 X-ray chest after treatment by Stilboestrol. The appearance of the lung fields is now within normal limits.

interest.

Improvement was noted on 27.4.44 and by 5.7.44 there was only ill-defined induration at the site of the primary, the glands were no longer palpable and there was some improvement in the chest as shown by X-ray. By 8.1.45 the lung fields were within normal limits (see plate 4) and the local condition remained stationary. However on 18.1.45 osteolytic defects were evident on an X-ray film of the pelvis. Her condition gradually deteriorated after this and she was not seen again in the Department. She died on 8.12.45.

Case No. 14,493 Mrs. M.P.

This patient had a carcinoma of the right breast treated in the usual way by simple mastectomy and X-ray therapy in October and November 1941, when she was 57 years old. She remained well until 20.7.44 when she developed skin nodules, a gland in the opposite axilla, diffuse metastatic involvement of both lung fields (see Plate 5) and widespread patchy osteolytic metastases in the pelvis. Stilboestrol dipropionate 5 mgm. b.i.d. was prescribed on 22.7.44 and by 31.8.44 the skin nodules and the gland had disappeared. X-ray films taken on 29.9.44 showed that the lung metastases had disappeared (see Plate 6) and that there was more sclerosis/

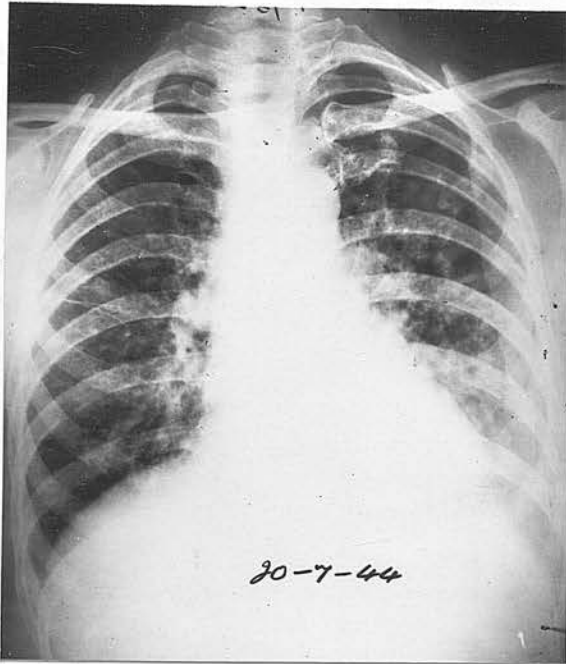
sclerosis around some of the bony metastases.

Stilboestrol was continued on alternate months and the patient remained well until 26.2.45 when two of the skin nodules again became prominent. The local condition deteriorated gradually. The patient was last seen on 26.7.45 and she died in December 1945.

Plates/

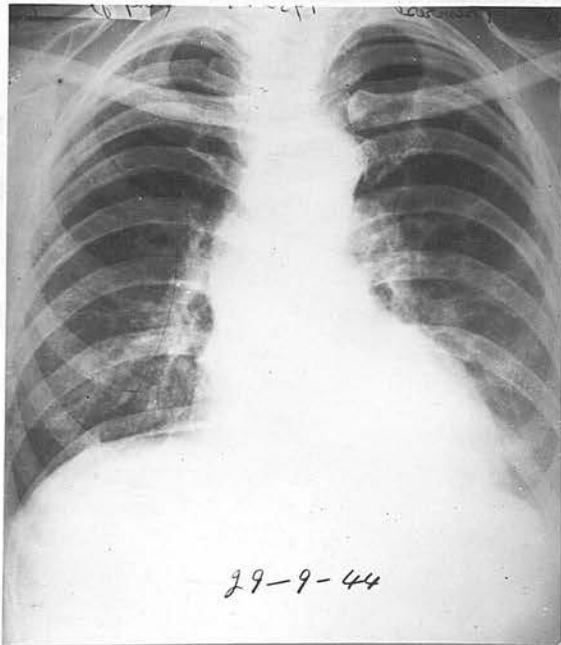
Mrs. M.P. Case No. 14,493

Plate 5



20.7.44 X-ray chest before administration of Stilboestrol. There is diffuse metastatic involvement of both lung fields.

Plate 6



29.9.44 X-ray chest after treatment by stilboestrol. The diffuse metastatic involvement in the lung fields has disappeared. There is still some prominence of the left hilum.

Average Survival after first date of giving
Stilboestrol

Grouped according to response.

Table IX.

Response	Survival in Months
A - good	29.76
B - fair	19.34
C - none	9.94
D - adverse	6.51
E - withdrawal response	26.90

As with ovarian irradiation it would appear that stilboestrol and oestradiol have an effect in prolonging life where recurrences and metastases have regressed or disappeared, but again this is only a very general statement, and there are many notable exceptions, as was well demonstrated in the case of Mrs. M.C., who after a dramatic initial response died eight months after starting stilboestrol. Her history is given in more detail.

Case No. 15,445 Mrs. M.C.

The patient had had a radical excision for carcinoma of the left breast on 8.4.40 when she was 65.

She remained well until November 1941 when she noticed/

noticed a swelling in the left axilla. On 14.5.42 this swelling was incised and blood-stained fluid escaped. The lining of this cyst proved to be malignant on histological examination.

In June 1942 the patient received a course of X-ray therapy to the left chest wall and axilla. On 27.9.43 she was found to have skin nodules and glands in the left side of the neck which were treated with X-ray therapy without success. By 3.2.44 there were numerous nodules on the anterior and posterior aspects of the left side of the chest. There was massive infiltration of the lower neck on both sides and on the left side the induration extended as far as the submaxillary region (see Plates 7 & 8). There was a small left-sided pleural effusion and osteolytic metastases in the region of the left sacro-iliac joint.

The patient was started on stilboestrol dipropionate on 9.2.44 receiving 5 mgm. b.i.d. and by 9.3.44 the skin nodules had practically disappeared and there was some sclerosis in the bony metastases. Further improvement took place until by 19.4.44 she was virtually well on clinical examination. Stilboestrol was continued but was reduced to 5 mgm. a day on 3.5.44 (see Plates 9 & 10 for condition on 3.5.44).

At the beginning of July 1944 however, the patient/

Mrs. M.C. Case No. 15,445

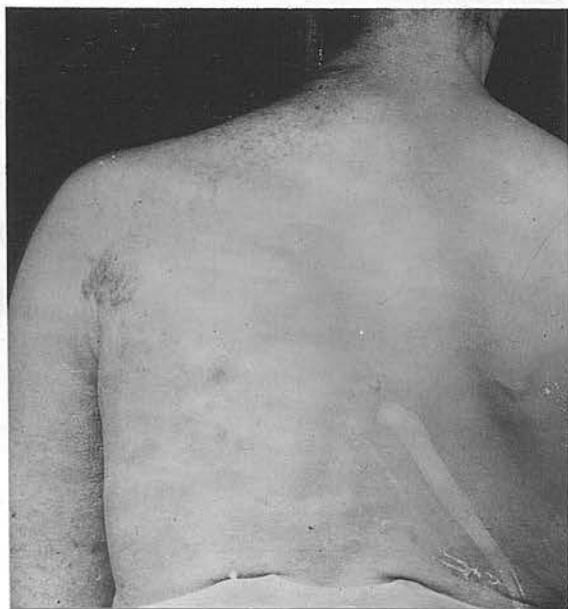
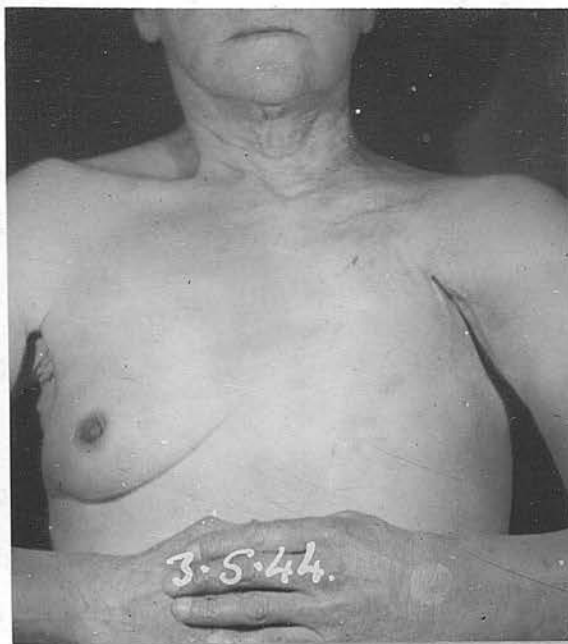
Plates 7 & 8



3.2.44 Clinical photographs taken before administration of Stilboestrol showing skin nodules on chest wall and swelling in the left side of neck.

Mrs. M.C. Case No. 15,445

Plates 9 & 10



3.5.44 Clinical photographs to show disappearance of skin nodules and swelling of neck after treatment by stilboestrol.

patient developed pain in the left shoulder and blisters appeared over the skin.

The stilboestrol was stopped but her condition rapidly became worse and she died on 16.10.44.

It seems as though in some cases, after the good response has passed, the final decline is more rapid than in a case which has not been treated with stilboestrol.

Among patients showing an adverse response, one lived 20 months after receiving stilboestrol. Of course in her case, the hormone was discontinued at once when the adverse effect was noted.

Dosage.

The optimum dosage of stilboestrol dipropionate was found to be 5 mgms. twice a day. Higher dosage did not improve the response, and, on the other hand if the patient proved intolerant, lowering the dosage minimised, but did not completely relieve the symptoms. The only indication for lower dosage was in those cases with a pleural effusion, where 5 mgm. b.i.d. sometimes caused sufficient water retention to embarrass the patient's breathing by increasing the volume of the effusion.

Where dimenformon was used, 5 cc. containing 5 mgm. was given twice a day. None showed a good response/

response, and it would seem that the optimum dosage has yet to be found. None showed any upset following the administration of this product.

Incidence of Symptoms produced by Stilboestrol dipropionate.

169 patients had no symptoms attributable to the hormone while taking stilboestrol. Many of the remainder had symptoms which however did not inconvenience them.

Of all the symptoms two classes could be distinguished:-

1. Those symptoms due to the side effects of stilboestrol.
2. Those attributable to the adverse effect of the drug on the disease.

1. Nos. of those with the various symptoms due merely to the side effects of Stilboestrol.

Vaginal discharge	3	Headache and muscle pains	3
Intermittent menorrhagea	2	Rash	1
Menorrhagia on withdrawal of drug	27	Palpitations	3
Menorrhagia while taking stilboestrol	22	Dizziness	4
Amenorrhoea (pre-menopausal patient)	1	Oedema of arms or legs	6
Initial nausea (and occasional vomiting)	56	Tiredness and sleepiness	6
Diarrhoea	4	Incontinence (due to diuresis on withdrawal of hormone)	4
		Increased dyspnoea (in cases with pleural effusion)	2

2. Nos. of those with symptoms related to the adverse effect of Stilboestrol on the disease.

Complete intolerance because of constitutional upset	4
Increased pain at the site of bony metastases	9
Acute mania (due to advance of cerebral metastases)	1
Pain in opposite breast	2

When a patient showed a good or fair response to stilboestrol and its administration was to be continued for some time, it was found more satisfactory to give it intermittently e.g. 5 mgm. b.i.d. on alternate months. In this way a more prolonged response seemed to be obtained, there was less constitutional upset and less risk of withdrawal menorrhagia.

Consideration of Sub-divisions of the preceding Group of Cases.

As stated already, this group of 279 cases which has been considered, comprises all those who received stilboestrol or oestradiol at any time; some received stilboestrol only and some received stilboestrol plus some other form of treatment such as ovarian irradiation. These groups will now be considered separately.

1. Consideration of cases receiving stilboestrol dipropionate only. They received no other hormone, nor were they given ovarian irradiation.

Table X/

1. Consideration of cases receiving stilboestrol dipropionate only. They received no other hormone, nor were they given ovarian irradiation.

Table X.

Total number of cases = 110

Results grouped according to response, age and survival

Response	Nos.	%	Average Age (yrs)	Average survival after Stilboestrol (mths).
A - good	17	15.45	68.2	28.80
B - fair	26	23.64	67.27	19.26
C - none	56	50.91	55.75	8.68
D - adverse	10	9.09	52.50	5.00
E - withdrawal response	1	0.91	63.00	9.00
	110	100%		

These figures correspond fairly well with those given for the whole group in Table . The percentage of good responses is higher, 15.45% as compared with 9.63%. There are two possible explanations for this - a) of the whole group of 279 cases, many of these which did not respond to stilboestrol were naturally tried on other preparations. They have been excluded from the present series of 110 cases receiving stilboestrol only. b) Cases receiving ovarian irradiation at some time prior to the administration of stilboestrol did not show any very good responses. This group will be considered separately next.

Consideration of Cases receiving Ovarian Irradiation prior to the Administration of Stilboestrol dipropionate.

Of the original 279 cases, 55 received ovarian irradiation first before stilboestrol.

The group is further subdivided into two:-

1. In 29 patients ovarian irradiation was given as part of the first treatment as a prophylactic measure, and then stilboestrol was given later for recurrences or metastases where further surgery or radiotherapy was impracticable.

The average time between ovarian irradiation and stilboestrol administration was 16.7 months (extremes were 3 and 44 months).

2. In 26 patients ovarian irradiation was given as a treatment for recurrences or metastases. The majority were pre-menopausal and it was hoped that castration would alter the course of the disease. A few were post-menopausal but the treatment was carried out to see if any effect would be obtained from eliminating any remaining ovarian function.

The average time between ovarian irradiation and stilboestrol administration in this group was 7.48 months (extremes were 2 and 17 months).

The average age of the whole group of 55 was 51.2 yrs. and 29 were pre-menopausal.

Response to Stilboestrol in relation to age.

Table XI/

Response to Stilboestrol in relation to age.

Table XI.

Response	Total Nos.	Nos. with group "F" withdrawn	% with group "F" withdrawn	Average Age (yrs.)
A - good	0	0	0	-
B - fair	5	5	11.91	57.00
C - none	25	25	59.52	50.44
D - adverse	9	9	21.43	50.80
E - withdrawal response	3	3	7.14	50.75
F - uncertain	13	-	-	-
	55	42	100%	

It would appear to be significant that no case in this group showed a sufficiently good response to warrant classification in the "A" category. There may be several explanations for this.

- a) The average age of the whole group is only 51.2 years and so the proportion likely to respond is correspondingly lower, and it may have happened by the laws of chance that none of the relatively few post-menopausal women included was of the type likely to show a good response.
- b) The menopause may not have been fully established when stilboestrol was given. It is known that the normal menopause is not complete for several years.
- c) An artificial menopause may differ from a normal menopause/

menopause. Normally there is a gradual slowing down of all reproductive activity whereas when the ovaries are inactivated by X-rays before the change of life, other parts of the endocrine system such as the suprarenal cortex may take over part of their functions and produce oestradial or related substances.

- d) It is possible that a normal non-irradiated ovary may be necessary for the production of a good response with stilboestrol treatment.

For similar reasons, the percentage of adverse responses is also higher than one might expect, 21.43% as compared with 3.21% in Table .

Of the 5 patients showing a slight response, 4 had had ovarian irradiation as part of the first treatment i.e. prophylactically. One had had it as a treatment for metastases in glands but without success. Their ages ranged from 38 to 70, the average being 54.4 years, and three of their number had not reached the menopause when ovarian irradiation was given.

The responses were not marked. Three had some reduction in the size of the local recurrences and glands for a period of only two months, one had diminution in the size of glands for six months and in the last, glands remained stationary in size for thirteen months.

of/

Of the 26 patients who received ovarian irradiation for metastases, 6 showed some response to this treatment. When this response wore off, stilboestrol was tried. In 3 there was no response to stilboestrol, in 1 a pleural effusion was made worse and in the last 2 stilboestrol had to be stopped because of the rapid deterioration in the patient's condition. One of them had excessive pain in bony metastases and the other showed such advance in orbital metastases that the drug had to be discontinued within 24 hours.

Consideration of Cases where treatment by dienoestrol was prescribed irrespective of other hormone treatment given.

Table XII.

Grouped according to response and survival after Dienoestrol

Response	Total Nos.	Nos. with group "F" excluded	% excluding group "F"	Survival after Dienoestrol (Mths).
A - good	2	2	6.25	44
B - fair	3	3	9.375	9
C.- none	23	23	71.875	17.62
D - adverse	4	4	12.5	9.5
E - withdrawal response	0	0	-	-
F - uncertain	7	-	-	-
	39	32	100%	

Table XIII.

Response	Nos.	Average Age (yrs)	Relation to the Menopause.
A - good	2	67.00	Both post-menopausal
B - fair	3	60.67	All post-menopausal
C - none	23	59.04	5 were pre-menopausal 4 had had O.I.* and 1 surgical castration.
D - adverse	4	45.75	All were pre-menopausal but 1 who had had O.I.
	32		

* Ovarian Irradiation.

The points noted here were:-

- 1) The relatively smaller numbers showing a good or fair response as compared with those in the stilboestrol group.
- 2) The age distribution is similar. The older women and especially those past the menopause tend to do better than the younger and pre-menopausal.
- 3) Where the drug has been of value in giving a very good response it also appears to have prolonged life. There has been no effect in those showing only a slight response.

Dosage.

The dosage used in 29 cases was 1 mgm. three times a day, and in 10 cases, 5 mgms. three times a day/

day. The incidence of symptoms caused by the drug was very low. One patient who received 5 mgm. thrice daily complained of flatulence, and two receiving 1 mgm. thrice daily had nausea and vomiting. Four had withdrawal vaginal bleeding.

The four patients who responded adversely had increase of pain in metastases. It is of interest that one of these had previously shown a good response to ovarian irradiation. The adverse effects produced by dienoestrol were obvious in 24 hours and were noted when the drug was tried again later.

Of those who did not respond:-

1. One showed a very good response to stilboestrol.
2. Four showed a fair response to stilboestrol.
3. One responded to a slight degree to testosterone.

Relation to Pathology and Site of Metastases.

The figures have been examined and although the numbers in each group are very little there is apparently no correlation between response and histological type nor between response and site of metastases.

Consideration of Cases receiving Triphenylchloroethylene irrespective of other hormone treatment given.

Total Cases = 6

Of these 6 cases, 5 had received routine treatment/

treatment in the first instance, namely, simple mastectomy followed by X-ray therapy, and one had received only a single palliative X-ray treatment as the first treatment.

Three had secondary skin nodules, four had enlarged lymph glands and one had metastases in the lungs.

The average age of the group was 63 years.

The dosage given was 0.5 gms. twice a day and only one patient was upset by it. She developed nausea and vomiting.

No case was made worse by triphenylchloroethylene, but only one showed a slight response. This will now be described in more detail.

Case No. 15,575 Mrs. C.S. aet 70.

This patient had a carcinoma of the left breast with mobile enlarged glands in the same axilla. A simple mastectomy was carried out on 23.5.42 and the tumour was found to be a glandular carcinoma showing a moderate scirrhous reaction. Operation was followed by routine X-ray treatment to the chest wall and axilla. On 28.5.46 she was found to have a recurrence in the same axilla and metastases in the lungs. She received ovarian irradiation on 28.5.46 but showed no response to this.

On 23.8.46 she was started on triphenylchloroethylene 0.5 gm. twice a day. Within a month the recurrence in the axilla became softer and less well-defined/

defined and for four months the lung metastases did not appear to progress. After February 1947, however, she became gradually weaker and she died on 25.5.47.

Consideration of Cases receiving Ethisterone (androhydroxyprogesterone) irrespective of other hormone therapy given.

Total Cases = 7

This drug was supposed to have an action opposite in some ways to that of stilboestrol and it was accordingly given a) to women who had not yet reached the menopause as it was thought that they might show an adverse response to stilboestrol, and b) to post-menopausal women who had already shown an adverse response to stilboestrol.

There were 5 in the pre-menopausal group, 4 of whom had had ovarian irradiation 9 - 13 months previously. There were 2 women past the menopause. The average age of the group was 46.4 years.

None showed a good response, and 3 were apparently made worse by the drug, 2 post-menopausal and 1 pre-menopausal. There were 4 different histological types of tumour among the cases considered.

Here again the group is too small to allow of definite conclusions being drawn.

Consideration of Cases receiving Testosterone Propionate in 1949 - results assessed up to 31.1.50.

The total number of cases in this series was 30.

The/

The average age was 50, extremes being 33 and 71.

It was found that the responses had to be graded slightly differently, on account of the remarkable improvement in the general health which might occur irrespective of the local response.

The results are therefore as follows:-

Table XIV

	Nos.	%	Average Age
A. General health improved and all evidence of local disease gone	1	3.33	50
B. General health improved, pain relieved or very slight regression in local disease while treatment continued.	7	23.33	48.2
C. General health improved, but disease advanced steadily	8	26.67	45.28
D. Deterioration in general health and apparent acceleration of disease	13	43.34	52.1
E. Intolerance of drug	1	3.33	43
	30	100.00	

The dose used was 50 mgms. of testosterone propionate daily, given intramuscularly. Treatment was continued for 3 to 4 weeks, and if the patient's condition seemed to warrant it an implant of the drug was then carried out. Dose of the implant was from 400 to 600 mgm. In this series 9 patients received an implant, the patient in group A, all in group B and one out of group C. The one case showing/

showing a good response was a woman of 50, who had had a simple mastectomy followed by X-ray therapy in September and October 1947 for a carcinoma of the right breast with mobile glands in the same axilla. She had ovarian irradiation at the time of the first treatment. (The menopause had been brought about artificially by the insertion of intrauterine radium in 1944). In September 1949 she was found to have a mobile glandular mass in the right axilla, and received testosterone propionate 50 mgm. a day from 5.9.49 to 4.10.49. A 400 mgm. implant was inserted into the abdominal wall on 21.10.49.

When she was seen on 8.10.49 the recurrence had disappeared, and she was well both locally and in her general health when last seen at the end of January 1950.

Of the cases receiving temporary benefit, one who was comatose and was thought to have cerebral metastases was improved sufficiently to be able to attempt cross-word puzzles. When seen three months after commencement of treatment with testosterone, she was found to have metastases in the dorsal spine and a large pleural effusion. At post mortem 2 months after that, she was found to have generalised metastases including a large sub-tentorial deposit.

Two others showed temporary diminution in the size/

size of the primary tumour when testosterone was given as the first line of treatment. In one of these bone metastases, which were originally of mixed osteolytic and osteoplastic type, became more osteoplastic. In the other a large pleural effusion did not cause any further respiratory embarrassment under treatment, but fluid was removed at increasingly longer intervals. Benefit lasted 2 and 5 months.

Two others showed temporary disappearance of recurrent nodules for a period of a month.

The last one experienced relief from bone pain, but X-ray evidence showed that there was no change in the bone metastases.

Among those who showed no response, there were patients with local recurrences and metastases in bone, glands, lungs, liver, eye and brain.

The patient who could not tolerate the drug was a woman of 43 with cerebral metastases. She developed very severe vomiting and only received 150 mgm.

Again in this group of cases, there was no apparent correlation between the histological type of the tumour and the degree of response.

Of the 30 patients treated since May 1949, 12 have already died, the average survival period being 2.83 months after the commencement of treatment (extremes were 1 and 5 months). Of these, one patient/

patient was apparently made worse and 9 showed no response. The other two showed a temporary response.

Apart from the one patient who could not tolerate the drug and who only had 150 mgm., no one was upset by the treatment. Indeed the reverse was the case in 53.33%, where the general health was improved. With the dosages given, signs of masculinization was seen in only 2 patients, both of whom developed facial hirsutes and hoarseness. These patients were aged 35 and 37 and the hoarseness passed off on cessation of the injections. The hirsutes was very slight, but was more persistent. One patient aged 64 developed a mild acne which also disappeared when the testosterone was stopped.

During treatment four patients who were still menstruating developed amenorrhoea. Periods recommenced 1 - 2 months after stopping the injections.

There was no apparent connection between the degree of response and previous hormone treatment.

Eleven had no previous hormone treatment and 6 out of these were pre-menopausal. It is interesting to note that one of these so-called 'pre-menopausal' woman who was only 33 had had amenorrhoea for 5 months before treatment. At post-mortem both ovaries were found to be secondarily involved.

Nineteen/

Nineteen had had previous treatment of one kind or another. One had had an artificial menopause brought about by radium several years before, she developed carcinoma of the breast. Ten had ovarian irradiation prophylactically as part of the first treatment and 7 had ovarian irradiation as a treatment for recurrences, one of these showing a good response and one a fair response.

One patient had had ethinyl oestradiol before with no response.

In all these various categories, there were patients showing a fair response and some showing no response.

The results in this group may be summarised briefly. No really dramatic response occurred but there was a remarkable improvement in the general condition of about half the patients while they were receiving testosterone injections. Such responses as occurred were not related to the age of the patient, nor did previous hormone treatment have any effect.

Discussion.

Results in the present series compared with those in the literature.

The results in this series are, for the most part/

part, in agreement with cases reported in the literature.

Oophorectomy and
Ovarian Irradiation.

The effects of castration may be considered in the first place. In this series, the effect has been brought about by X-ray therapy in the majority of cases, only 9 patients having a bilateral oophorectomy. Some observers think that there may be a difference in physiological action between the two methods (Smith 1936). However the results, as quoted, are comparable, and the only reasonable difference is that surgical removal might be more permanent, ovarian function possibly returning to some extent after irradiation.

Another point to be considered in this series is that the assessment of results was based on cases where the response to ovarian irradiation was uncomplicated by other treatment given at the same time. Not all published results have been assessed in this way (Ahlbom 1930).

Dresser (1936) reported that 30% of pre-menopausal patients showed regression of metastases, especially skeletal metastases, the relief from symptoms lasting 2 to 3 years. About 43.3% were relieved of pain. In none of the post-menopausal patients was regression noted.

Here/

Here there were 16.67% of good responses and 19.04% of fair responses, that is a total of 35.71% of pre-menopausal patients showed some degree of improvement. This agrees with Farrow's conclusions (1944). He reported that approximately one-third of pre-menopausal patients benefited from ovarian irradiation, relief lasting 6 to 24 months. The average survival in the present series was 23.67 months.

All types of metastases were found to regress, skeletal and extra-skeletal. This has been the general finding (Farrow 1944 and Smith 1936).

The Response to
Oestrogenic Substances.

The findings in the cases treated with oestrogens also agree fairly well with those reported previously.

In this series 52.02% showed a favourable response to stilboestrol dipropionate. Ellis et alia (1944) found that 41 out of 168 showed some improvement i.e. 24.4%. In many later series the patients have been selected to some extent, in that only older women and those with extra-skeletal metastases have been treated. The figures are, therefore, hardly comparable. The Council on Pharmacy and Chemistry (1949) report improvement in about half the cases.

All/

All observers are agreed that good results are to be hoped for only in older women. Opinions differ as to what is meant by the word "older". Hermann, Adair and Woodard (1947)^(1,2) suggest 60 years and over. The Council on Pharmacy and Chemistry in their 1947 report put the limit as 5 years after the menopause and Adair et alia (1949) as 2 years after the menopause.

In the cases treated here, the youngest patient showing a good response was aged 58, and the average age was 68.00 years. All were post-menopausal.

It is stated by Nathanson (1947) that in younger patients the disease appears to be accelerated on some occasions by the oestrogens. It was certainly found here that the percentage of younger women was greater in the group showing an adverse response, being 47.82%, compared with 0% among the good responses. However, there were exceptions, as one patient of over 70 showed an adverse response. Taylor et alia (1948) also reported the case of a woman of 67 who became worse following treatment.

A fact not generally reported, but noticed here, was that a few patients (3.21%) show a slight response when stilboestrol is stopped. However, Farrow (1944) stated that he noted growth inhibition in bone metastases following withdrawal of both oestrogens/

oestrogens and androgens. Among the withdrawal responses here, 50% were seen in local recurrences, 28.6% in glands and 21.4% in bone metastases, but whether this type of response was really more common in bone it would be difficult to say because of the smallness of the numbers under consideration.

As noted by other observers (Taylor et alia 1948 and Paterson 1949), some patients showed a general response in respect of all manifestations of the disease, while in others some metastases regressed while other advanced or new ones appeared. This phenomenon has not been satisfactorily explained.

Most reports stress that soft tissue metastases are more likely to respond than skeletal metastases. As stated already, however, no significant difference was seen here in the percentage of different metastases in each type of response. In 5 there was a dramatic response in skeletal secondaries as illustrated in the reproduction of the X-ray films of a representative case in Plate II page There was no doubt about the repair which had occurred in bone. Paterson (1944) reported relief from pain in bone. Taylor et alia (1948) could produce no controlled X-ray evidence of response in bone lesions because localised X-ray treatment was often combined with oestrogen therapy. They thought though that fewer new bone metastasés appeared during/

during treatment with the oestrogens, and therefore, that the hormone had a retarding effect.

The part which the histological type of the tumour plays in determining the response seems to be debatable. In cases where it was possible to correlate the two, the general opinion seems to be that tumours which have responded have been of the undifferentiated and more cellular type (McWhirter, Paterson 1944 and Haddow 1944). Paterson suggested that the reason that no scirrhus tumours showed a response was that the drug had less easy access to the cancer cells, because of their poor vascularity.

It has been found in this group that well-differentiated adenocarcinomata and also tumours showing a scirrhus reaction have responded, and there was no real correlation between pathology and response. It must be remembered however, that the pathological reports were issued by a number of different pathologists in different parts of the country. This is in some ways not so satisfactory as a review of all the slides by one pathologist.

Changes in the histological picture, such as a diminution in the number of mitoses and pyknosis of nuclei, after treatment with the oestrogens were noted by Haddow (1944). In 4 cases in Edinburgh, biopsies were carried out after the administration of stilboestrol. None of these showed any clinical response/

response, and, as expected, the histology showed no features of interest.

As has been suggested already, there may be a more fundamental difference between tumours, a difference which is not apparent on histological examination alone.

The drug found most generally useful was the synthetic oestrogen, stilboestrol dipropionate, because of its cheapness, ease of administration and the high proportion of good results produced. The dosage used has been of the same order as that used elsewhere - 2.5 to 5 mgm. twice or thrice daily.

Paterson (1944) reported some responses using triphenylchloroethylene and later writers (Hermann, Adair and Woodard 1947¹⁾ have tried ethinyl oestradiol which is supposed to be less toxic.

Whether the effect of ethinyl oestradiol on breast carcinoma will be as marked as that of stilboestrol remains to be seen, because dienoestrol, though less toxic, appears to be also less efficacious. Nevertheless Rae (1948) using both stilboestrol and dienoestrol, reported similar effects with the two drugs, the dose of stilboestrol being 10 to 15 mgm. a day, and the dose of dienoestrol a third of this.

It may be that, as with other groups of drugs, many more related compounds have yet to be tried, and one may be found to be less toxic, and of greater/

greater value than stilboestrol.

The Council on Pharmacy and Chemistry published a further report in August 1949 on this aspect of the subject. A co-operative study had been carried out by a group of workers using different oestrogenic compounds and different dose levels. The only drug used extensively was diethyl stilboestrol and the investigation is to be pursued further. They reported 60% showing improvement with this drug, but there was some selection of cases, as the patients were mostly over 60 and suffering from soft tissue metastases.

The most troublesome side effects produced by the oestrogens are usually reported as nausea, vomiting, uterine bleeding (usually on withdrawal) and various clinical manifestations of oedema. Only occasionally are those reactions sufficiently severe to require discontinuance of the therapy. The administration of stilboestrol intermittently e.g. on alternate months tends to minimise endometrial hypoplasia and reduce the incidence of severe vaginal bleeding. This method was also advocated by Taylor et alia (1948).

All reactions occurred sufficiently frequently to stimulate a search for compounds having the desired therapeutic action without any of the unpleasant side effects.

The/

The Response to Progesterone.

With regard to progesterone, Loeser (1941) tried it, but found that, as in the present series, no good results were produced.

The Response to Testosterone.

The reports in the literature on the efficacy of testosterone are very variable, more so than in the case of the other forms of hormone treatment. All gradations of response have been reported. Farrow (1944) noted a deleterious effect, Nathanson (1944) observed no effect at all, and various later workers (Adair 1947, and 1949, and Kaae 1949) reported a proportion of good responses.

All are agreed that testosterone may act like a tonic on many patients and produce a beneficial effect on the general health. The patients often appear fuller in the face and of a better colour, and they have a brighter outlook on life. This appears to be a non-specific effect and is not confined to sufferers from malignant disease.

Part of this has already been explained by the stimulating effect of the hormone on the protein metabolism, and by its effect on sodium and potassium metabolism leading to water retention and an increase in weight. (Cutler & Schlemenson 1948).

53.33% in this series showed this good effect, but apart from the one case it only continued as long/

long as the drug was given and may have been partly psychological in nature. Sylven and Hallberg (1947) gave it as their opinion that even the relief from pain might have a psychic basis, although they admitted that the development of new metastases was often preceded by a fresh onset of pain.

It seemed in the present series as though deterioration was more rapid, once the initial good effect had passed off.

Haagensen (1948) noticed that in about one-third of cases there was relief from pain and an improvement in the general health.

It has been generally acknowledged that improvement with testosterone therapy may occur at any age, and that has been the experience here. The type of response bears no relationship whatsoever to age.

Most observers have reported that the favourable responses occurred in skeletal metastases. Kaae (1949) while stating that the best effect was seen in bone, also reported one case where an ulcerated primary tumour healed and glands disappeared, the patient remaining well thereafter for 9 months. Adair et alia (1949) gave testosterone propionate 100 mgm. thrice weekly to 70 patients with metastases to bone or soft tissue or both. Objective improvement occurred in 19% of 48 patients with skeletal metastases, and in 15% of 54 patients with extra/
extra/

extra-skeletal metastases. Hermann and Adair (1947) report one case where the primary tumour and glands remained healed for 3 months.

In the present series, improvement when it did occur, was mainly in soft tissue metastases, although one case showed increased osteoblastic activity in metastases which were previously of a mixed type.

The possibility that dosage and duration of treatment have an effect on the response must be considered. Good results have been reported using as little as 50 mgm. twice a week, but most use doses of the order of 100 to 300 mgm. twice a week. (Adair, Kaae 1949)

Adair et alia (1949) using 100 mgm. thrice weekly found that the cumulative dose at the time of improvement varied from 500 to 11,400 mgms. and approximately half these were of the order of 3000mgm.

The Council on Pharmacy and Chemistry in their 1949 report, came to the conclusion that responses might be obtained with doses as low as 50 mgms. thrice weekly but that there was no real advantage to be obtained by the use of doses over 150 to 300 mgms. weekly. From the point of view of total dose, it seemed that the maximum response occurred when about 3000 mrm. had been given. Only 32% of patients with soft tissue lesions received relief of symptoms with less/

less than 2 months' therapy, whereas 65% received relief after more than 2 months' therapy. Patients with pain from bony metastases received relief sooner, 80% after 1 month's treatment. Only 30% obtained relief with less than 1 month's treatment.

From the point of view of objective response, soft tissue lesions might show a favourable response after 1 month's therapy but the majority of osseous lesions which showed regression did not respond until after the fifth month of treatment.

It would seem therefore that treatment was not given over a long enough period in Edinburgh. The maximum period of daily injections was 1 month and no patient received more than 2000 mgms. Most of the patients were treated either as out-patients or in their own homes. The rest occupied beds in busy medical or surgical wards. In all cases there were considerable practical difficulties in the way of prolonging treatment beyond a month, unless a dramatic response had convinced everyone that the method was worth while.

Toxic effects in this series have therefore, been the exception. Only 2 patients showed slight facial hirsutes and hoarseness. With higher dosages these effects were more marked and oedema and hypercalcaemia have been observed in a number of cases.

Treatment/

Treatment of
Male Cases.

Reports of cases of breast cancer in men treated with hormones are naturally very rare. The results in women are sufficiently confusing even with figures which are numerous enough to analyse, but in the male the position is less clear and these are only mentioned for the sake of completeness. Leucutia (1946) and Nathanson (1947) reported a beneficial effect from orchidectomy. Paterson (1944) stated that the only man in her series treated with triphenylchloroethylene showed regression of the disease.

The only male case in this series was aged 36 and was made rapidly worse by stilboestrol.

Consideration of Mode of Action.

It would obviously be of the greatest interest and importance to discover the manner in which these effects are produced. Where a good response is obtained it gives a patient a few extra years of comfort when she has otherwise no prospect of relief. Besides this, there is always the possibility that if the mechanism were understood, much might be done to improve the results and possibly even solve the problem connected with all forms of malignant disease.

At the outset however, it must be stated that
the/

the mechanism of action is still obscure, and all explanations put forward are purely speculative.

Theories propounded
in the Literature.

Various theories have been put forward in the past.

Schinzinger based his suggestion for oophorectomy on his impression that in older women breast tumours were slower growing. He reasoned that castration by prematurely aging the patient as it were, would slow down the rate of growth. Basically this idea seems to be that normal ovarian secretion is a stimulus to the malignant cell in a breast cancer.

Beatson's theory was that carcinoma breast was caused by ovarian dysfunction and that oophorectomy removed the cause. He combined with this treatment the administration of thyroid extract because he thought it augmented the effect. It is interesting that later developments do suggest that the thyroid may take part in the inactivation of the oestrogens. Van Horn (1933) gave large doses of dessicated thyroid daily to rats. It caused a loss of weight and persistent anoestrus. It required 3 rat units of oestrone to produce vaginal cornification.

Since the breast is subject to hormonal control related to sexual and reproductive functions, it is reasonable to suspect, as Beatson did, that disturbances of these functions may play a major part in the genesis of breast cancer. The results of much/

much statistical and some experimental work have left no room for doubt that this is indeed the case.

In the first place it has been found that single women are more liable to develop breast cancer than married women. The mortality rates in England and other countries show an excess of deaths among the unmarried, when due regard is paid to the proportion of single women in the population. Lane-Clayton's figures from the surgical literature (1924) showed that in England 15% of the female population over 40 years of age were single, but 22% of the breast cancers were from single women. The figures in other countries are comparable. The Registrar-General's analysis of deaths in 1930-32 showed the death rates of mammary cancer to be markedly greater for single than for married women in all age groups over 35.

Another point is that breast cancer in child-bearing women is inversely related to fertility. Lane-Clayton's comparisons of cancerous and control series of married women showed an unmistakable difference of fertility. Even when allowance was made for cases in which the disease itself may possibly have diminished child-bearing capacity, it was found that women who ultimately developed mammary cancer bore 22% fewer children than in the control series. In the control and cancerous series the/

the average numbers of viable children per married woman were 4.97 and 3.53 , a ratio of 1.4 to 1.

Furthermore, there is evidence, statistical as well as experimental, to show that failure to suckle, premature weaning and possibly other errors of lactation play a part in the production of breast cancer. In her 1926 report, Lane-Claypon found that complete failure to suckle and the habit of suckling for a very long period were both more common in the cancer series than in the control series.

Thus it would seem that thwarted reproduction and thwarted lactation seem to predispose to cancer; normal reproduction and lactation are the prophylactics.

Another argument used to show that ovarian function has a bearing on the development and course of carcinoma of the breast was that the disease seemed to be accelerated by pregnancy (Emge 1934 and Rosenthal 1939).

It is difficult to confirm this from the consideration of patients seen in Edinburgh. There is no doubt that many pregnant patients present with an advanced form of the disease, but this seems to be due to the general tendency in the medical profession to overlook the possibility of malignant disease in all young patients. It has also/

also been pointed out by Smith(1936) that one of the advantages of ovarian irradiation is that it prevents further pregnancies which might be supposed to cause deterioration in the patient's condition. Actually in Edinburgh it has been found that the 4-year survival rate of patients treated for carcinoma breast who subsequently became pregnant was 47.62%, which compares favourably with the 47.92% which is the 4-year survival rate of all cases treated between the years 1941-45. However it must be pointed out that a considerable degree of selection comes in when subsequent pregnancies are considered because naturally the more advanced cases are either unlikely to become pregnant or die in the first year or so after treatment.

Further work has been done to confirm this idea, originally put forward by Beatson, that an abnormal endocrine state exists in patients who develop breast cancer. Nathanson (1944) attempted the study of the steroid metabolism in such patients by investigating the urinary excretion levels of sex hormones but his results were not conclusive. Although Nathanson was not clear that such a study gave one any idea of blood levels, rate of secretion or destruction or utilisation of these hormones by the tissues, he came to the conclusion that there was a difference in excretion of oestrogens/

oestrogens and 17-ketosteroids in patients with breast cancer. The individual excretion of oestrogens and 17-ketosteroids may be different, and the normal ratio may be upset. The findings were not taken as characteristic of carcinoma, but as evidence that deviations from the normal were occurring, probably as a result of a disturbed metabolism.

It seems clear from all these observations that the ideas of the earlier workers were well-founded and that the endocrine state may either play a part in the genesis of breast cancer or at least suffer an alteration in a patient with such a tumour. This does not help us to discover how an artificial manipulation of the endocrine system is to be utilised in treatment. It seems reasonable however, to remove all ovarian function in younger women.

Haddow's theory that the oestrogens act by specific inhibition of tumour cells is also interesting. It was based on a comparison of the similarity between these compounds and the carcinogenic hydrocarbons. Some components have both oestrogenic and carcinogenic properties, but one side is always predominant. He also noted changes in the histological picture such as diminution in the number of mitoses in cases showing a good clinical response.

This/

This idea of a specific local action is supported by other facts. For example, it is known that the oestrogens may be fixed selectively in certain tissues such as rapidly growing or inflamed tissues (Bonnelli 1935). It is possible therefore that they are fixed in certain tumour cells.

It is true also that in small doses, under certain experimental conditions, oestrogens in small doses may cause inhibition of cell growth. Tyslowitz (1939) found that daily injections of 5 mgm. diethylstilboestrol to dogs brought on an agranulocytic anaemia in 25 to 50 days.

Another connection between local tumour metabolism and the action of the oestrogens was pointed out by Fishman and Anlyan (1947). They found that the β -glucuronidase activities of various human tumour tissues were higher than in normal tissue. β -glucuronidase is supposed to participate in the metabolism of the oestrogens, and the increased activity was thought to be a metabolic response to a high concentration of oestrogen in the tumour.

There has, however, been no work on the effect of the oestrogens on breast tumours comparable to the work of Huggins on carcinomata of the prostate, and/

and the effects do not appear to be nearly so clear cut.

Although a local effect is seen in the tumour, it may be due to a more general action of the hormones and the result of some more central effect. Naturally the breast would show some local response to such a general reaction. One would also expect to see cell changes in a metastasis which is regressing for any reason even after the application of X-ray therapy.

Zondek's reason for using ovarian hormones was that they produced an inhibition of the anterior pituitary with diminution in the output of the gonadotrophic and growth hormones. The first brought about what he termed a "hormonal castration". The second possibility has not been investigated, and it is doubtful how active is the production of growth hormone after puberty.

The reasons for using testosterone were based on the work of Lacassagne and others, which showed that oestrogenic substances induced breast cancer in mice and that male hormone was in part antagonistic to the action of the oestrogens and therefore apparently suitable for the treatment of breast cancer. It was realised, of course, that testosterone too, will inhibit the gonadotrophic hormone of the anterior pituitary and bring about a medical castration.

Conclusions/

CONCLUSIONS REACHED AS TO THE MODE OF ACTION.

As a result of an extensive perusal of the literature and an analysis of cases personally observed, I have come to the conclusion that the most likely explanation for the many different responses is that on some occasions tumour inhibition can be brought about by artificially altering the endocrine status of the patient. In this way the method itself is not all important, but rather the change in the hormone balance in any particular patient.

For example in a young patient who has not reached the menopause, the natural ovarian hormones are circulating in the body. Oophorectomy or ovarian irradiation causes a sudden withdrawal of these substances, and the altered conditions naturally have a particular bearing on breast tissue whether normal or malignant.

The withdrawal of natural oestrogenic substances results in an increased output of the gonadotrophic hormone of the anterior pituitary. This stimulates extra-gonadal sources of oestrogen activity such as the supra-renal cortex so that in the course of time the hormone balance of the body is partly restored and the beneficial effects of castration wear off.

In an older patient, say a woman who is five or more years past the menopause, the endocrine balance is/

is different. There is little or no natural circulating oestradiol, and the addition of female sex hormones whether natural or synthetic changes the natural state once again. After the passage of time the body, and, in particular, the breast cells become readjusted to the new state of affairs and the good effect of stilboestrol passes off.

The actual mechanism of the action of stilboestrol in such a patient may be produced through an effect on the anterior pituitary. The administration of large doses of oestrin was found by Zondek to produce enlargement of the pituitary in male rats, that is in rats not normally subject to the action of such large amounts of an oestrogen. That this may occur in the human species is exemplified by the case reported by Zondek (quoted already) in which oestradiol benzoate was given to a woman for metastases from a carcinoma breast. After death, her pituitary was found to weigh 710 mgm. as compared with a normal of 595 mgm. (the average for nullipara of her age according to Zondek) and microscopical examination revealed an adenoma or localised hyperplasia of eosinophilic cells.

It may be therefore, that the action of stilboestrol brings about a profound change in the pituitary with perhaps disturbance of other factors such as the growth hormone.

In/

In a pre-menopausal patient a drug such as stilboestrol would cause inhibition of the gonadotrophic hormone, so suppressing natural ovarian secretion, but not bringing about a true "castration". "Castration" could not be said to be complete while an artificial oestrogenic substance is circulating in the blood. Consequently there is not the same profound change in the endocrine status and no useful therapeutic effect is produced.

Some patients, as noted already, show a slight response when stilboestrol is stopped. This response occurs, in general, in younger women (the average age was 58 years) and possibly there was some natural oestradiol being produced. The sudden withdrawal of stilboestrol would cause an increased output of gonadotrophic hormone and a suppression of this natural oestrogenic activity. It was this alteration which produced the temporary regression in the tumour. The response in such cases was not marked and did not last for more than a month or two.

The administration of androgens is a different matter. In a younger patient, of course, they bring about a complete medical castration by inhibition of the anterior pituitary and from this point of view would be expected to have a similar action to that of/
of/

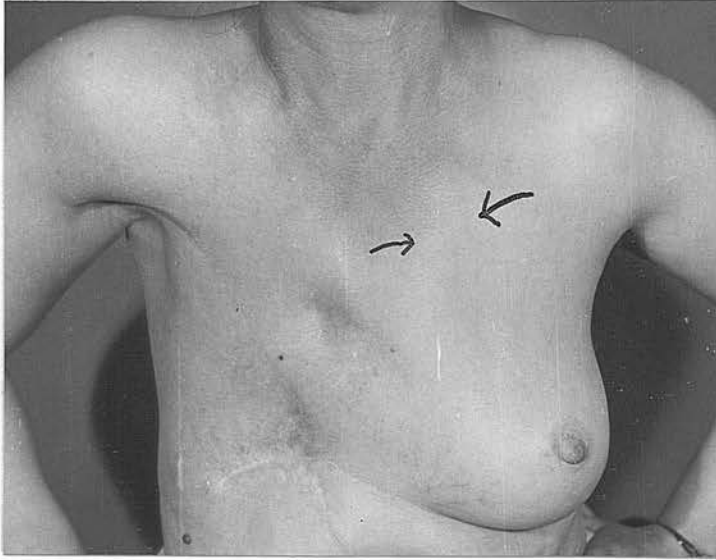
of oophorectomy or ovarian irradiation.

In addition, however, if one accepts the theory that it is the change in the endocrine status of the patient which produces the good effect, then obviously the administration of male hormone to a female patient must have a profound effect in this respect and must upset the normal ratio considerably. From this point of view one would expect androgen treatment to be effective at any age and that has been found to be the case.

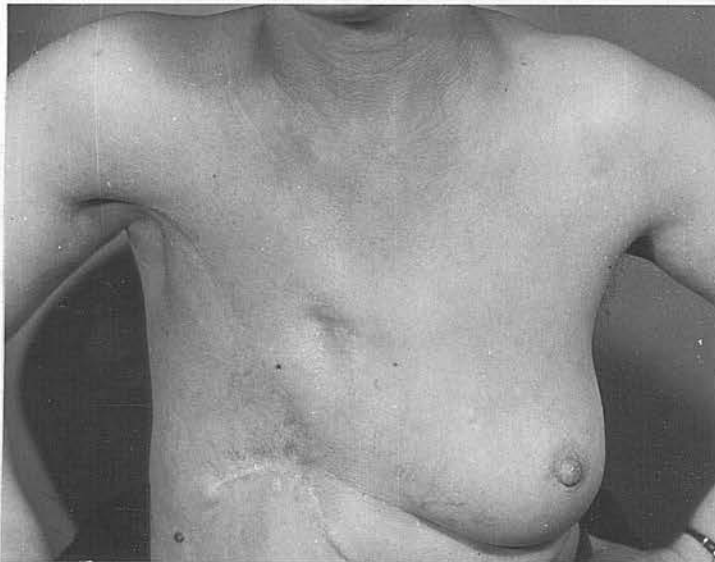
As the anterior pituitary plays an important part in regulating the endocrine status of the patient, an alteration of this status would probably be produced by irradiating the pituitary itself. It had been found that after hypophysectomy in mice bearing transplants of a mammary cancer, the transplants continued to grow but at a reduced rate (Korteweg and Thomas 1939). Accordingly pituitary irradiation was tried for the first time in Edinburgh in October 1949, and the first case treated proved highly successful. This was a woman of 51 who was only 8 months past the menopause. She had had a radical mastectomy and X-ray therapy in 1939 for carcinoma of the breast. She developed a fixed recurrent mass 6 x 4 cm. over the sternum in September 1949. X-ray therapy, to a dose of 3,000r was given to the pituitary over a period of three weeks/

Mrs. C.B. Case No. 10,583

Plates 11 and 12.



30.9.39 Clinical photograph to show recurrent mass overlying sternum.



25.11.49 Clinical photograph taken after completion of pituitary irradiation. Recurrent mass is no longer visible.

weeks. The swelling became half the size during the course of treatment and had disappeared by the end of treatment. She remained well when last seen on 13.1.50. (See Plates 11 & 12 p. 102).

This obviously calls for further investigation, and this is being carried out at present.

An explanation must now be sought for the failures. By every method so far outlined the successes are not much more than 30%. Even if each method were applied only to cases deemed suitable there would still be a high percentage of failures.

It is possible that the metabolism of these substances may be different in different patients. Some patients may have a more stable endocrine system, less easily upset by artificial means or capable of great compensatory changes e.g. after an oophorectomy there may be in some patients a more rapid adaptation by the suprarenal cortex so that oestrogenic substances are again produced in considerable amounts.

This, however, may not be the whole explanation. There are several other factors which may modify the response and these will now be considered.

In the first place the type of tumour may have an effect on the responses produced.

Haddow (1944) suggested that the tumour called "carcinoma of the breast" might in reality comprise several/

several categories.

Paterson (1949) also made the same suggestion, even going so far as to say that a tumour might produce an "anti-hormone" or inhibitory factor antagonising the action of the oestrogens. She supported this theory by her findings that in general, patients who did not respond did not show such a complete degree of keratinisation in the vaginal epithelium. This latter is the normal physiological response in post-menopausal women to treatment with one of the oestrogens and, if this action were inhibited it suggested that there was a general inhibition of all oestrogenic activity. It seemed as though some substance were being produced, either in the tumour or elsewhere, which was able to nullify the actions of one of the oestrogens.

Further, the presence or absence of the ovaries would appear to have some effect on the response produced when the oestrogens are used, but it is impossible to go further than to suggest that a normal ovary, whether pre- or post-menopausal may be essential for the production of a really good response.

Finally, another factor which might interfere with the physiological actions comprising the basis of response is the state of the liver. The liver/

liver inactivates ovarian oestrogens (Golden and Severinghaus 1938). In hepatic cirrhosis there is an excess of free oestrogenic substances in the blood. Westerfeld (1940) says tyrosinase, on incubation, inactivates oestrone, oestradiol and diethylstilboestrol. Zondek and Sklow (1942) believe the inactivation is caused by an enzyme oestrinase - similar to but not identical with tyrosinase. Jaiger (1948) found that in mice fed on a diet deficient in vitamin B₁, the degradation mechanism of oestrogens in the liver was impaired. It was not the B₁ deficiency but the concomitant inanition which was found to be the cause.

In addition to the more common causes of liver dysfunction, patients with carcinoma breast may have metastatic involvement of the liver. How this would affect the response is not known exactly, but it is perhaps significant that no patient with clinical evidence of liver involvement showed any response at all to any of the methods of treatment outlined. It is reasonable to suppose that toxic manifestations might be more common in such patients.

POSSIBLE/

POSSIBLE LINES FOR FUTURE INVESTIGATION.

It is obvious that a great deal of work remains to be done on the subject. In the first place it would be useful if simple and accurate means of estimating the excretion products of steroid metabolism could be devised and applied in the first instance to a determination of the normal values in pre- and post-menopausal women. A further series might be done on women of all age groups suffering from carcinoma breast, and lastly on non-cancerous and cancer patients receiving different types of hormone therapy. These results, correlated with liver function tests might help to clear up some of the problems of steroid metabolism in malignancy.

A wider range of hormone preparations might be tried systematically and different levels of dosage of each preparation tested.

As the effects may be brought about through an inhibition of the anterior pituitary, it would be useful to treat a series of patients by means of X-irradiation of the pituitary. This is now actually being carried out in the Radiotherapy Department.

Present
Position

In conclusion the position must be cleared at the present moment so that patients may have the benefit of the treatment most likely/

likely to help each individual case.

The indications appear to be fairly simple. Ovarian irradiation would seem to be the most efficacious in women who are at the menopause or 2 - 3 years past it and in all pre-menopausal women. It is easily carried out and indeed may be given without any delay as a single treatment to an out-patient. There is little immediate upset, although subsequently the patients experience all the discomforts of the menopause.

For women who are two or more years past the menopause, one of the synthetic oestrogens such as stilboestrol dipropionate would seem to be the best. The tablets are easily taken at home under the supervision of the patient's own doctor.

Once a good response has stopped or where no useful effect has been obtained, it has been found that other lines of treatment usually fail also. However, it might be worth while trying testosterone, if possible for a period of two months or more. Because of its expense and difficulty of administration it is not recommended in the first place, because ovarian irradiation appears to be as satisfactory in younger women and one of the oestrogens in the older women.

SUMMARY/

SUMMARY.

An attempt has been made in this thesis to study the application of endocrinology to the treatment of carcinoma of the breast.

The extensive literature on the subject has been reviewed, and it has been shown how the knowledge gained from animal experiments has been added to the information obtained from clinical observation, so that at the present day we have some idea how to help patients who are otherwise beyond the reach of any other form of therapy.

The development of the work in Edinburgh has been outlined. Over 500 cases have been reviewed in the present series and the conclusions reached are in the main in accord with those reported in the literature. These may be briefly summarised.

There is no indication that hormone therapy cures carcinoma of the breast, and even from a palliative point of view, radiotherapy to localised metastases is more likely to give a better result and more lasting relief.

Where hormone therapy is indicated it has been found that ovarian irradiation is of value in premenopausal patients. 10.07% of all patients treated showed a good response and 11.41% a fair response.

The/

The administration of stilboestrol dipropionate gives a good response in 9.63% and a fair response in 20.18%. Women in the late fifties and over respond best. The dosage found most useful was 5 mgm. twice a day on alternate months.

Other synthetic oestrogens, dienoestrol and triphenylchloroethylene, have been found to have some beneficial effect. They do not seem to have such a marked action as stilboestrol, but the numbers, especially in the triphenylchloroethylene group, are small.

No response was seen in any case treated with progesterone, but here again the numbers were too small to allow of a definite opinion.

Testosterone, with or without bilateral oophorectomy, may be of value in women of all ages. In this series no dramatic response was found, but again the numbers so treated was small and the total dosage - about 2000 mgm. - was smaller than the doses reported in the literature as most likely to give a good response.

Various findings either do not agree completely with those reported in the literature or have not been specially noted before.

All types of metastases, including those in bone, have on occasions responded to stilboestrol. Radiological evidence of response in bone has not been found in the literature.

Using testosterone, response in soft tissue metastases has been found here more frequently than in osseous metastases. Others have reported response more frequently in bony lesions.

The response to stilboestrol has been found to be less favourable after ovarian irradiation. This has not been noted particularly before.

No correlation has been found here between response and histological type.

The possible mode of action has been discussed. Various theories put forward by other observers have been mentioned.

It has been concluded that the most likely mode of action is by an alteration of the endocrine balance of the patient. The stability of the endocrine status therefore determines response in the first place. This may be modified by an inherent disturbance of steroid metabolism such as is occasioned by liver dysfunction. It may also be modified by previous ovarian irradiation.

A further important factor lies in the nature of the tumour itself. Some tumours may be more sensitive than others to changes in the balance of the sex hormones.

Finally various suggestions are made as to how the subject may be further studied and the work extended.

In/

In conclusion my thanks are due to Professor McWhirter for permission to review these cases.

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