HORMONES AND HUMAN BREAST CANCER

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by

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THERE IS no question that true growth regression of human breast cancer may follow the therapeutic administration of sex hormones. It is equally certain that hormone deprivation brought about by surgical castration, bilateral adrenalectomy, hypophysectomy, or a combination of the first and second operations can produce a similar effect. It is also reasonably certain that the administration of oestrogenic substances in small doses has been followed by true acceleration of tumour growth. Neither hormone administration nor deprivation has yet effected an undoubted cure, and the responsiveness of this growth to hormone treatment varies within the widest limits—from total resistance at one extreme to spectacular but transitory growth regression in a small minority of instances at the other. At the present time about one-third of all patients show a significant clinical response, but in quoting this disappointing and very approximate figure we must remember that hormone therapy is often reserved for inoperable or recurrent cases, usually in the late stages of the disease, and that bilateral adrenalectomy has not yet been practised on a large enough scale to decide if its early promise will be fulfilled. It appears, therefore, that there is a relationship, probably a very close one, between certain endocrine organs and the growth of some, but not necessarily all, human breast cancers.

If we examine this relationship more closely we encounter some formidable uncertainties. It is often difficult, sometimes impossible, to explain the results of hormone therapy on the basis of our present knowledge of endocrine physiology, and we have no really conclusive evidence that any hormone is the primary, exciting or initiating cause of human breast cancer, although experimental evidence is strongly suggestive. All we can reasonably assume, in our present state of ignorance, is that *when some human breast cancers have come into being, their continued existence depends to an uncertain degree, and for an uncertain time, upon a continuous supply of one or more sex hormones. This state of affairs has been called Hormone Dependence.*

Hormone Dependence

In human pathology those cancers of the breast and prostate which show undoubted histological regression after, and clearly related to, hormone deprivation or administration are regarded as hormone dependent. In women who develop oestrogen-secreting tumours of the ovary five or more years after the menopause, oestrogen-dependent hyperplasia

of the previously atrophic endometrium and breast is always found, and in a significant percentage of such cases an oestrogen-dependent adenocarcinoma of the uterus develops. A smaller, but still significant, number of such patients develops cancer of the breast.

Foulds has described a spontaneous mammary carcinoma occurring in hybrid mice which provides a remarkable example of hormone dependence. This tumour appears during pregnancy, grows rapidly and reaches its maximum size at or near parturition. In some animals growth stops abruptly immediately after parturition and, in a remarkably short time, apparently disappears completely. Unless pregnancy supervenes there is no sign of recurrence. Should the animal become pregnant, however, the same cycle of growth during pregnancy and regression at parturition will be repeated in this and in subsequent pregnancies. In other animals, after a few cycles of growth and regression, the tumour breaks away from hormonal control and grows without interruption and irrespective of pregnancy. The tumours are usually multiple and whilst one may show the pregnancy cycle of growth, another in the same animal may grow without restraint. Similar periods of latency and growth, and the same unexplained variability of clinical response to hormone therapy, are commonly seen during the natural history of human mammary carcinoma.

There is no doubt that the post-natal development, growth and maintenance of the stroma and duct system of the normal pre-menopausal human breast, under physiological conditions, is controlled by an ovarian oestrogen, probably *oestradiol.* This powerful steroid hormone is produced by those cells of the Graafian follicle which are derived from the ovarian stroma. The formation and secretory activities of the follicle are under the over-riding control of the gonadotrophic hormones of the adeno-hypophysis, which act as the appropriate and effective stimuli to follicle formation and oestrogen production by the mature pre-menopausal ovary. The fertile epithelial cells of the duct system of the breast, especially those lining the small terminal ductules, are, under normal conditions, extremely sensitive to the mitogenic and growth stimulating action of ovarian oestrogen, and exhibit a high degree of avidity for this hormone when it is circulating in the blood. Oestrogen avidity and sensitivity are inborn genetic characteristics of the epithelial cells of the uterus, Fallopian tubes, vagina, and breast ducts, and it is clearly justifiable to describe the normal growth and development of the epithelia of these accessory sex organs as being oestrogen-dependent.

Oestrogen Production after the Menopause

With the exception of growths arising in the larger ducts, most human breast cancers, especially the more malignant ones, arise in the oestrogen-sensitive epithelium of the small terminal ductules, and it may well be that the cells of a breast cancer, having an origin in cells possessing such deeply rooted genetic characteristics, also need an oestrogenic substance for their continued multiplication. **This hypothesis is the rational background for the hormonal treatment of human mammary cancer.**

We cannot, however, jump to the conclusion that such an oestrogenic tumour-maintaining hormone is produced by Graafian follicles because the majority of human breast cancers arise during or after the menopause, which usually results in total follicular atrophy. On the other hand, it may be that some tissue remaining within the follicle-free ageing ovary remains sensitive to pituitary gonadotrophic hormones and is capable of continued oestrogen production. Alternatively, it is possible that some organ other than the post-menopausal ovary is responsible for the continuous production of an oestrogenic hormone.

Oestrogen Production by the Post-menopausal Ovary

The cells of the ovarian stroma may be the source of post-menopausal oestrogen. After all, these cells make a very substantial contribution to the formation of the early Graafian follicle, and, being present in maximum numbers during the peak period of oestrogen production, it is highly probable that oestrogen production is their major function. On the other hand, the granulosa cells which eventually outnumber them are concerned with the formation of the corpus luteum.* There is some evidence that certain cells of the ovarian stroma become prominent and active after the menopause but this problem merits more attention from the histologist than it has yet received, and an investigation of the minute structure of the stroma of the post-menopausal ovary under physiological and pathological conditions might prove to be a rewarding enquiry.

Oestrogen Production by the Adrenal Cortex

The other alternative is that after menopause, and under the stimulus of a pituitary trophic hormone, some organ other than the ovary produces a steroid oestrogenic hormone which is capable not only of maintaining the epithelium of the duct system of the normal breast but also the growth of a mammary cancer originating in this oestrogen-dependent epithelium. The only organ having the first and second of these qualifications is the adrenal cortex, extracts of which are known to be oestrogenic. It is well established that, after gonadectomy, oestrogen in small quantities continues to be excreted in the urine. It is also known that if castration is carried out in young immature animals this strongly tends to be followed, after an interval of time, by hyperplasia of the adrenal cortex. During this interval, and as the result of castration, the uterus, vagina and breast fail to develop and remain small and infantile. If adrenal hyperplasia develops and becomes well established, these tissues then show clear and unmistakable evidence of powerful oestrogenic stimulation and undergo the typical structural metamorphosis associated with sexual maturity. It seems, therefore, that the hyperplastic adrenal cortex induced by castration releases oestrogen in relatively large amounts. The above experiment becomes invariably successful when castration is carried out

* Ovarian tumours producing oestrogen are often referred to as granulosa-cell tumours. This usage is not in accord with modern views regarding the cellular origin of ovarian oestrogen.

at a very early age in infantile mice of certain in-bred strains : the degree of adrenal cortical hyperplasia is then quite remarkable and under these highly artificial conditions the operation of a genetic factor is generally assumed. It may appear to be a foolish presumption to apply the effects of castration on in-bred infantile mice to the problem of hormonal maintenance of breast cancer in the post-menopausal human female, but these experiments certainly establish the biological principle that *following removal of the gonads the adrenal cortex is capable of becoming a rich source of oestrogen and, to this extent at least, of taking over one of the major functions of the ovary.* It is certainly true that no constant association between human breast cancer and enlargement or hyperplasia of the adrenal cortex has ever been described. It must, however, be borne in mind that to maintain experimental endocrine hyperplasias and neoplasias, the essential factor is a continuous supply of hormone, the effective dose being often surprisingly small (Burrows and Horning, 1952). Supporting evidence that continuous oestrogen production by the adrenal cortical tissue may occur is furnished by naturally-occurring human disease.

An appreciable percentage of tumours arising in the human adrenal cortex produce steroid sex hormones in large quantities. In the very large majority of instances the hormone produced is an androgen, and its effect is to produce virilism. In a small minority when cortical tumours occur in men, the effect is feminising and the urine contains remarkably large quantities of oestrogen, which disappears on removal of the tumour, to re-appear as its metastases develop.

There are good reasons, therefore, for regarding the cortices of the adrenal glands as potentially bi-sexual accessory sex organs, and in this connection we should remember that as glandular derivatives of the coelomic mesothelium they share a common embryological origin with the ovaries. These and other cogent reasons which so strongly suggest that the adrenal cortex may become a potent source of either male or female sex hormones, led Huggins to advocate and practise the operation of bilateral adrenalectomy for prostatic and mammary cancer.

Our primary hypothesis was that some cases of breast cancer are oestrogen-dependent. We may now enlarge this hypothesis by assuming that whilst some pre-menopausal breast cancers may be ovarian oestrogen-dependent, an uncertain number of post-menopausal cancers may be adrenal oestrogen-dependent. The idea that some post-menopausal cancers may be ovarian oestrogen-dependent, the hormone being produced by the stroma cells of the follicle-free ovary, needs further support and must remain an open question.

The Menopause and Breast Cancer

To what extent does the investigation of the human patient support the hypothesis of hormone dependence ? In answering this question we may look for evidence from two sources. First, from the statistical

relationship, if any, between the menopause itself and the incidence of breast cancer ; secondly, from the results of the clinical investigation of post-menopausal women for evidence of continuous endogenous production of oestrogen.

Incidence of Mammary Cancer during the Menopause

The number of women in a large population developing breast cancer shows a decided decline during the years of the menopause. It is not easy to collect statistically reliable data regarding the onset and incidence of diseases which are not notifiable but the relationship is clearly shown in the curve (Figure 1) constructed by Clemmesen from information of exceptionally good quality collected by the Danish Cancer Registry. The average age of onset of the menopause in Denmark is 48 years, and the sharp upward trend of the pre-menopausal incidence is interrupted and shows a significant decline at this age. The sharp upward trend is not resumed until the menopause is over, approximately four years later. If we were to indulge in justifiable speculation regarding this downward trend in cancer incidence as ovarian function is declining, we might suppose that breast cancer before the menopause is ovarian oestrogen dependent, that during the decline in oestrogen production during the years of the menopause a significant number of potential cancers fails to be so maintained, whilst following the menopause an increasing number of cancers becomes adrenal-dependent as the adrenal cortex comes into play. These curves also clearly show the higher incidence of breast cancer in single as opposed to married women. It is also significant in this regard that breast cancer becoming clinically recognisable just before the onset of the menopause tends to show transitory regression during the menopause. On the other hand, mammary cancers arising well within the years of the menopause are certainly no less malignant than those which arise in the post-menopausal years.

The Post-menopausal Endometrium

What direct evidence have we that the post-menopausal woman may continue to produce endogenous oestrogen ? Novak and Richardson (1941) examined the uterus for endometrial hyperplasia in 137 unselected women two to fifteen years or more after the menopause. They attempted to eliminate " granulosa-cell " tumour of the ovary by omitting patients who had ovarian enlargement or uterine bleeding. Their figures are :—

Years after menopause	Total	Endometrium	
		Atrophic	Active
2 to 5	63	28	35
5 to 10	31	13	18
15 or more	43	21	22

(*i.e.*, endometrium active in 75 ; atrophic in 62.)

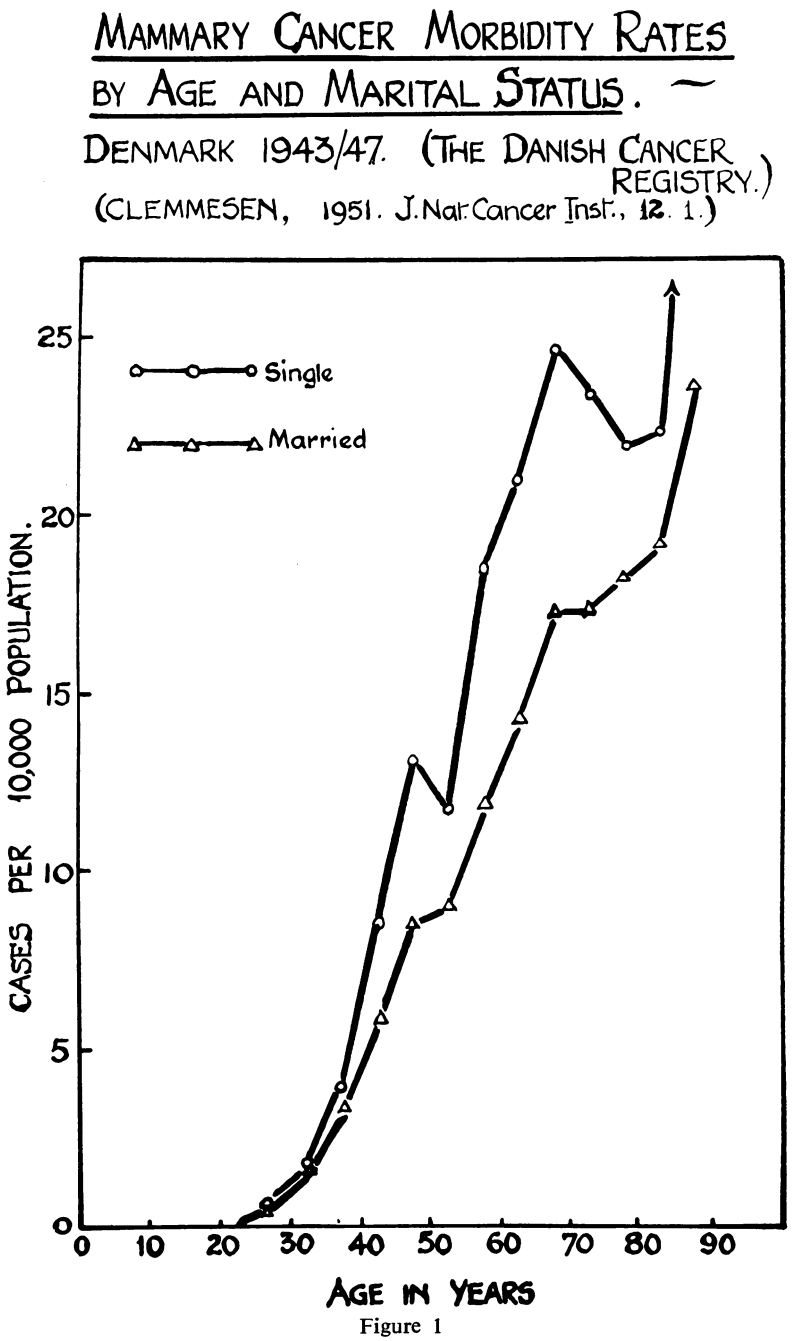
MAMMARY CANCER MORBIDITY RATES
BY AGE AND MARITAL STATUS. ~
DENMARK 1943/47. (THE DANISH CANCER REGISTRY.)
(CLEMMESEN, 1951. J. Nat. Cancer Inst., 12. 1.)
Single
Married
CASES PER 10,000 POPULATION.
0
5
10
15
20
25
0
10
20
30
40
50
60
70
80
90
AGE IN YEARS

Figure 1

A critical study of the sections of these active endometria showed in some individuals that, although hyperplasia was present, it was retrogressing or had become cystic and inactive ; in others, that the type and quality of the change did not justify regarding it as being the result of active oestrogen stimulation. At the lowest estimate, it was decided that of the whole group an oestrogen stimulated endometrium was present in about 30 per cent. The state of the endometrium showed surprising variations. In some women it was totally atrophic 18 months after the termination of the menopause. In others a typical oestrogen stimulated endometrium was encountered 30 years afterwards.

Stretton Young, working under the aegis of the Imperial Cancer Research Fund at the Royal College of Surgeons of England, investigated the vaginal mucosa in a series of normal post-menopausal women, using the vaginal smear technique and the Papanicolau stain. There was clear evidence of oestrogen stimulation in the vagina in 28 per cent. of 98 cases ; no evidence of stimulation in 54 per cent., and the state of the vagina was indeterminate in 18 per cent. The ages of the women in this series varied between 63 and 85, i.e., between 15 and 37 years after the termination of the menopause. On evidence such as this we may assume that about 30 per cent. of post-menopausal women continue to produce endogenous oestrogen whose probable source is the adrenal cortex.

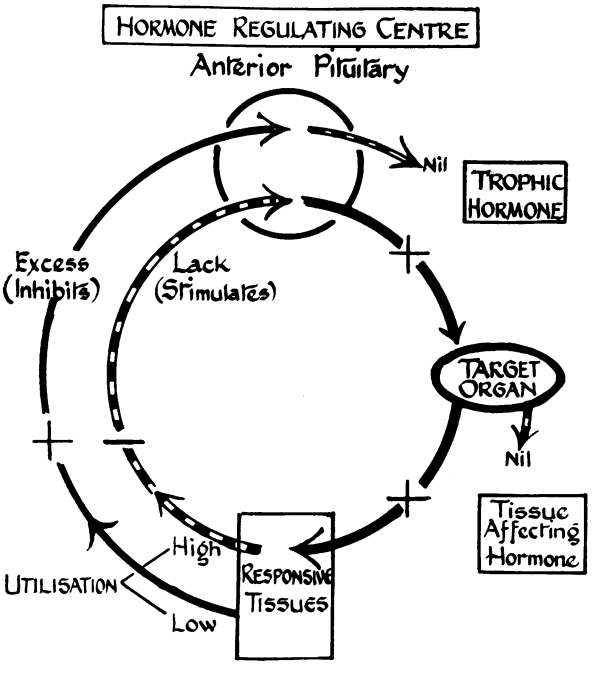

Figure 2

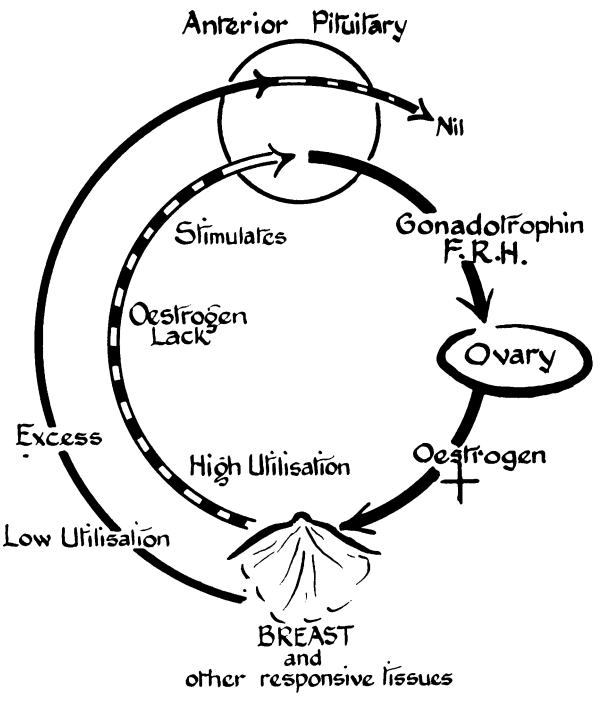

Figure 3

The Gonad-Pituitary Relationship

We must now consider the functional activity of the anterior pituitary or adeno-hypophysis during the years of high incidence of human breast cancer. May I remind you of the physiological mechanism by which the balance of function in the endocrine organs is maintained by the adeno-hypophysis acting as the *hormone regulating centre* ?

The gonads and adrenal cortex, together with the thyroid and pancreatic islets, may be regarded as *pituitary target organs* (see Figures 2 and 3), whose functional activity is under the dominance of the *trophic hormones* or trophins of the adeno-hypophysis. Each trophic hormone is the specific and effective chemical stimulus to its own target organ—pituitary gonadotrophic hormone, for example, to its target organ, the ovary. The stimulated target organs produce *tissue affecting* hormones, each of which is taken up exclusively by strictly appropriate tissues whose cells possess a high degree of specific avidity for the hormone and respond to it by a specific reaction. The stroma and duct system of the mature pre-menopausal breast, which has a high degree of avidity for oestrogen, is such a tissue.

The rate of utilisation of a tissue affecting hormone by its specific tissue depends on the needs of the body. Utilisation of ovarian oestrogen

by the breast, for example, waxes and wanes during the menstrual cycle and proceeds at a high level and becomes continuous during the first half of pregnancy. If tissue utilisation is high, the concentration of the tissue affecting hormone in the blood will fall, and *below a critical level the relative lack of circulating hormone constitutes the effective physiological stimulus to the release from the anterior pituitary of the appropriate trophic hormone* which stimulates the target organ to produce more tissue affecting hormone. On the other hand, if the utilisation of hormone by the tissue is low, the concentration in the blood will rise, and above a critical level the excess will inhibit the liberation of pituitary trophic hormone and output from the target organ of tissue affecting hormone.

Gonadotrophin Production after the Menopause

The stimulating effect of a relative lack of tissue affecting hormone on the adeno-hypophysis has a special application during and after the menopause, when follicle formation in the ovary ceases and the only cells which appear to remain active are those of the ovarian stroma. The atrophic post-menopausal ovary as a target organ then either ceases to respond to pituitary gonadotrophin, and ovarian oestrogen production falls to zero, or, if its stroma cells are responsive, to produce oestrogen in minimal quantities. *The absence or low level of concentration of ovarian oestrogen in the blood acts as a perpetual stimulus to the adeno-hypophysis for the rest of the patient's life.* The blood concentration of pituitary gonadotrophin rises to, and remains at, a high level and there is a continued and excessive excretion of the hormone in the urine (see Figure 4). It is quite remarkable that the activity of the adeno-hypophysis should be maintained in this way during the period of senility, however long this may last.

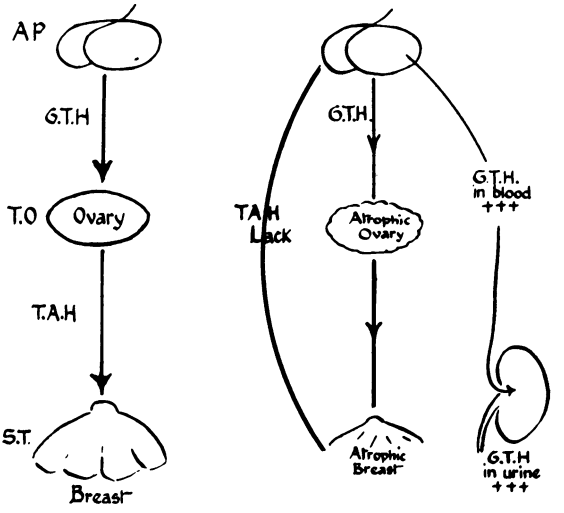

Figure 4

The blood and urine levels of gonadotrophin are therefore valuable indices of ovarian oestrogen production and their estimation should always form an essential part of the investigation of patients suffering from mammary cancer. Urinary estimations of excreted gonadotrophin, although of considerable service, are open to rather serious criticism and it is to be hoped that a method for estimating the concentration of this hormone in the blood will be devised in the near future. If oestrogen production is taken over by the adrenal cortex after ovarian atrophy this would not affect the high blood concentration of gonadotrophic hormone. It may (especially if it were vigorous) affect the blood level of anterior cortico-trophic hormone.

Effect of Large Doses of Oestrogen

Temporary clinical regression of human breast cancer has been repeatedly observed following the administration of large doses of oestrogen. Small doses may cause growth acceleration or have little or no clinical effect. In the light of the general principle that an excess of tissue affecting hormone will inhibit the discharge of trophic hormones from the adenohypophysis, it may well be that large doses of oestrogen, by maintaining a high level of oestrogen in the blood, inhibit gonadotrophin production by the pituitary. The unstimulated ovary cannot function, there is a significant fall in endogenous oestrogen production, and the inactive organ undergoes temporary disuse atrophy (Fig. 4). This sequence is well established in the case of other target organs. A very striking degree of atrophy of the adrenal cortex can be readily induced by the administration of A.C.T.H., and insulin administration in sufficient amounts will cause a striking degree of atrophy of the pancreatic cell islets. That this variety of experimental disuse atrophy has a wide significance in general pathology is illustrated by the severe degree of aplasia of the haemopoietic bone marrow which follows large and repeated blood transfusions in the rabbit, aplastic anaemia developing when the transfusions are discontinued.

Adrenal Oestrogen

Extracts of the adrenal cortex, in addition to a water soluble fraction which includes compound F and a potent amorphous fraction, also contain a series of benzene soluble steroids which have an alcoholic or ketonic grouping in the 17 position of their cyclo-penteno-phenanthrene rings. In addition to the corticosterones and deoxycorticosterones this series includes the adrenal androgens and oestrogens. Over-production of these sex hormones by the adrenal cortex will give rise to the presence of abnormally large quantities of their excretion products in the urine and to a decided increase in their number and complexity. A significant alteration in the excretion pattern of these substances therefore indicates the production by the adrenal cortex of steroid sex hormones in increased quantities.

The Pharmacological Action of Oestrogens

Oestrogenic Hyperaemia.—Active capillary hyperaemia with increased capillary permeability and oedema is an early and characteristic effect of oestrogen in those tissues which possess specific avidity, sensitivity and responsiveness to it. It is very probable that this preliminary action is responsible for securing a high local concentration of oestrogen in sensitive tissues. The local vascular response of acute inflammation would have a similar effect.

Oestrogen Sensitivity.—It has already been mentioned that specific sensitivity to oestrogen is an inborn genetic characteristic. Ectopic foci, autotransplants and homotransplants of oestrogen sensitive tissues retain the sensitivity of the parent tissue, and when such dislocated cells proliferate this characteristic is transmitted to their progeny.

Mitogenic Effect.—Given an adequate local concentration of oestrogen, its fundamental action is to increase the rate of multiplication of responsive cells. Bullough (1942-1950), in a series of cytological studies, has shown that this is achieved by a specific mitogenic effect. In an oestrogen treated tissue the number of mitoses in operation at any one time is greatly increased when compared with the resting tissue, whilst the duration of each cell division is very materially reduced.

Stroma Response.—An important aspect of oestrogen activity concerns the responsiveness of the mesenchymal stroma which carries the blood and lymph supply and supports the parenchyma of the gonads and accessory sex organs. An adequate response on the part of the stroma is obviously essential for growth, multiplication and differentiation of oestrogen sensitive epithelia. It is also essential that the stroma reaction should be limited to the oestrogen sensitive organ. We must conclude, therefore, that the gonads and accessory organs are supported by an oestrogen-sensitive stroma which may be directly stimulated by oestrogen or, in a less specific manner, by the initial oestrogen-induced capillary hyperaemia. In either case we must assume that if the cells of a mammary cancer are oestrogen dependent, the growth of its mesenchymal stroma is influenced to an equal degree by this hormone.

General Somatic Action of Sex Hormones.—There is no doubt that fibroblasts and osteoblasts will grow and multiply in response to oestrogenic stimulation in any tissue whose growth and development for the time being is oestrogen dependent. Such growth is clearly only a part of the well recognised general and metabolic action of oestrogens and androgens, both of which profoundly influence general body metabolism by promoting protein anabolism and calcium retention. Both hormones are responsible for the growth of epidermal, muscular and skeletal tissues peculiar to each sex. Consider the general effects of withdrawal of oestrogen after castration, or the menopause. There is a progressive decrease in the thickness of the skin, the size and tone of the muscles and the weight

and density of the skeleton. The last effect has a direct bearing on our subject.

The Osteoblastic Response.—Radiograms of the post-menopausal lumbar spine commonly show osteoporosis which not infrequently reaches such a degree that one or more vertebral bodies collapse. Such a lesion may be repaired or prevented by the administration of sex hormones, androgens being more potent in this respect than oestrogens. Osteoblastic activity and the formation of bone matrix is stimulated, calcium retention takes place, and new bone formation is induced. This effect of sex hormones on osteoblastic activity has a direct bearing on our problem as the administration of androgens is frequently followed by retrogression of the skeletal metastases of mammary cancer. This effect may, to some extent, be due to a direct action on the cells of the growth but it is not improbable that direct osteoblastic stimulation plays a significant part, for localised osteosclerosis of considerable degree in the neighbourhood of the metastases has often been observed.

Irregularity of Response to Oestrogen.—It is well recognised that the secondary sex organs, including the breast, do not respond uniformly to oestrogen stimulation. Some breast lobules give the impression of being unresponsive ; others show a minimal reaction ; in others it is vigorous. Whilst difficult to explain, this typical variation in reactivity may have some bearing on the localisation of hyperplasia and neoplasia in the breast.

The Investigation of Human Breast Cancer

There is no doubt that hormone-dependent human breast cancer may, by becoming hormone independent, acquire total resistance to all forms of hormone therapy at present available to us. *This transition is so common and unpredictable that the likelihood of its occurrence precludes the use of hormone therapy as the only or major form of treatment in any variety of breast cancer.* On the other hand, hormone therapy is quite clearly indicated and should be vigorously pursued as an essential therapeutic measure in the treatment of hormone dependent growths as soon as possible after radical surgery has been carried out. There is little to be said in favour of delaying hormone therapy until the growth has recurred or metastasised, for during the period of delay the growth may become hormone resistant. Furthermore, the disappointing results of radical surgery in human mammary cancer clearly show that excision of the growth is often incomplete.

How are we to decide whether a mammary cancer is hormone dependent, and, in the case of hormone dependent growths, can we come to any conclusion regarding the site of production of the hormone upon which the continued existence of the growth depends ? Neither the histological structure nor rate of growth of the tumour helps us to solve this problem, for rapidly growing and widely metastasising tumours are sometimes

very favourably influenced by hormone deprivation. At the present time the only easily available method in common use is that of therapeutic trial which is unsatisfactory from several points of view. It may involve a needless waste of time The effects of therapy are judged solely by an estimation of the size of the recurrent growth and its metastases by direct measurement or by radiology, both methods being rather crude and sometimes fallacious.

I would therefore like to suggest to you that whenever facilities are available, a serious attempt should be made to assess the functional state of the gonads, the secondary sex organs, the adrenal cortex and the adeno-hypophysis before hormone treatment is instituted, and that these investigations should be repeated at regular and frequent intervals during the course of treatment. It is my firm belief that for many years we have been so anxious to discover all we possibly can about the structure of the growth and its metastases that we have almost forgotten the soil in which it grows. The methods available for investigating the functional state of the endocrine organs are admittedly unsatisfactory, but will certainly improve, and the routine employment of a scheme of investigation such as the following would place the hormone therapy of mammary cancer on a rational basis, and should without question be carried out before submitting a patient to the hazards of such an operation as bilateral adrenalectomy :—

Ovarian Function

(1) Cytology of frequently repeated vaginal smears.
(2) Examination of frequently repeated uterine curettings.
(3) Histology of the excised ovaries to determine :—
    (*a*) Activity of the stroma.
    (*b*) Presence of latent metastases.*

Adrenal Function

(1) Repeated determination of the pattern of steroid hormone excretion in urine.
(2) Examination of excised adrenal for latent metastases.*

Pituitary Function

Repeated estimations of pituitary gonadotrophins.

Sir Thomas Beatson of Glasgow was the first to publish a clear description of the regression of breast cancer following oöphorectomy. He came to the following conclusion :—

" . . . *one of the values attached to oöphorectomy is that the effects produced seem to me to have their chief interest and importance in that they throw a light upon the nature of carcinoma as a disease.*" This conclusion is as true to-day as when it was written—43 years ago.

* Metastatic deposits of breast cancer too small to cause swelling or deformity are not uncommonly found in the ovary and adrenals in human mammary cancer.

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