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TREATMENT OF ADVANCED CARCINOMA OF THE BREAST*

BY

A. C. CROOKE, M.D., M.R.C.P.

Endocrinologist, United Birmingham Hospitals

Endocrine treatment of carcinoma of the breast has gone through a number of phases from hormonal therapy with androgens, oestrogens, and corticoids to oophorectomy, adrenalectomy, and hypophysectomy, each of which has led on occasion to dramatic improvement but none of which has been shown to be outstandingly the best. It is well known that some tumours of the breast are hormone-dependent while others are not, and that tumours which are hormone-dependent initially will eventually escape from dependence and progress inexorably despite further attempts to alter the hormonal environment. The reasons for these differences are obscure, partly because the factors which are responsible for mammary development and lactation are still not completely understood and partly because hormonal balance is difficult or impossible to assess adequately.

Hormonal Factors in Breast Development

Knowledge of the hormonal factors responsible for development of the breast has accumulated gradually over the past thirty years, aided particularly by the work of Folley (1956) and his group at Reading and by Lyons (1958) and his colleagues at Berkeley, California. These hormonal factors are now becoming more clearly defined owing to the use of experimental animals whose relevant endocrine glands have all been removed, and also to the use of chemically pure hormones. The hormonal factors are grouped broadly under mammogens and lactogens, terms which are in line with the well-known terms oestrogens, progestogens, and androgens.

Mammogens may be defined as hormones which, acting singly or in synergism with other hormones, will induce any of the three main phases of mammary growth—ductal, ducto-alveolar or lobular, and lactational; and lactogens as hormones which, acting singly or in combination with other hormones, will induce milk formation. The term lactogen therefore has a narrower connotation, and it is noteworthy that lactogenic hormone is itself a mammogen (see Diagram on next page). For this reason Lyons prefers the term mammotrophic hormone (M.T.H.), which is also in line with the other trophic hormones—gonadotrophic, thyrotrophic, and adrenocorticotrophic. Likewise the California group prefer to call growth hormone somatotrophic hormone (S.T.H.). S.T.H. is the other main pituitary mammogen. Both M.T.H. and S.T.H. are available as pure proteins by current standards. Both act on the breast in synergism with steroid hormones.

It is well known that oestrogens promote ductal growth in the breast, but they are quite incapable of preventing ductal atrophy which follows hypophysectomy in the young rat. Lyons has shown conclusively that they are dependent on the presence of S.T.H. to prevent this atrophy. S.T.H. is

also incapable of preventing ductal atrophy in the rat which is deprived of its sources of steroidal hormones. The two hormones are therefore said to act in synergism. It is remarkable that substitutes have been discovered for both hormones. The adrenal mineralocorticoid deoxycortone has the same action as oestrone when given in doses five hundred times as great by weight, and smaller amounts enhance the combined action of oestrone and S.T.H. S.T.H. can be replaced by long-acting insulin, but its action is less pronounced (Ahrén and Jacobsohn, 1956; Ahrén and Etienne, 1958).

S.T.H. and oestrogen are incapable of inducing the next stage of development of the breast, but lobular growth will occur in young castrated rats treated simultaneously with the corpus luteum hormone progesterone. This does not occur in the hypophysectomized rat, however, because progesterone, like oestrogen, requires a pituitary hormone as synergist. Lyons has shown that this is M.T.H. There are therefore at least four hormones which are essential for development of the breast up to this stage—oestrogen with S.T.H. and progestogen with M.T.H.—and it is remarkable that the body has no confidence in its ability to produce enough of them for all the requirements of pregnancy. As a result high concentrations of at least three are produced in the placenta, the production of S.T.H. by this organ being still questionable. It is interesting to speculate on the influence of this factor on carcinoma of the breast. Finally, in the rat which has been deprived of its pituitary, gonads, and adrenal glands the addition of an adrenal glucocorticoid like cortisol leads to better development, but still no milk is formed. Curiously, the thyroid gland appears to be unimportant for this development.

Milk Secretion

In the experimental rat, milk secretion depends on the continuation of treatment with M.T.H. and the withdrawal or great reduction of treatment with the sex steroids oestrogen and progestogen. In an animal deprived of its adrenal glands and gonads the addition of corticotrophin or a glucocorticoid like cortisol is essential. Six hormones are therefore ultimately necessary for the production of milk. The transfer of milk from the lobules to the larger ducts is initiated by the posterior pituitary hormone oxytocin, and the suckling stimulus is necessary for its delivery. Suckling probably causes the secretion of oxytocin.

Throughout the development of the breast the ratio of these various hormones to one another is important and is variable from species to species. For instance, in the oophorectomized goat whose pituitary is left intact oestrogen alone in suitable doses can cause extensive development of the udder with lactation, so that progesterone appears to be relatively less important in this species. The ratios of the hormonal factors required for the development of the human breast have still to be established, and clearly these may be of considerable value in the study of carcinoma of the breast.

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Oestrogens in Relation to Carcinoma

The conception of hormone-dependence of a carcinoma implies that the qualitative character or absolute or relative concentration of certain hormones is important for neoplastic growth, and extensive studies have been made of the concentration of various hormones in blood and urine in an attempt to correlate them with remissions or relapses of the disease. The oestrogens have received most attention partly because the various surgical procedures have been designed primarily to remove the source of oestrogens and partly because there are well-recognized methods for their measurement. The results of a number of investigations on urinary oestrogens were described in a series of papers read at a Conference on Endocrine Aspects of Breast Cancer held at the University of Glasgow in 1957 and published in its *Proceedings*. The methods are, however, by no means simple. There are two ways of dealing with them—by biological assay and by chemical determination.

At first sight the biological method would seem to be the method of choice because it is sensitive and it measures the total biological activity of oestrogens regardless of the

	Terminology	Anterior Pituitary Hormones	Ovarian Steroid Hormones	Auxiliary Hormones
Mammo-gen	Ductal growth	Growth or somatotrophic hormone (S.T.H.)	Oestrogen (e.g., Oestrone)	Corticotrophin or mineralocorticoid (e.g., deoxycortone)
	Ducto-alveolar or lobular growth	Lactogenic or mammatrophic hormone (M.T.H.)	Progestogen (e.g., Progesterone)	Corticotrophin or glucocorticoid (e.g., cortisol)
Lactogen	Lactation	Lactogenic or mammatrophic hormone (M.T.H.)	None	Corticotrophin or glucocorticoid (e.g., cortisol) (obligatory)
	"Let down"	Posterior pituitary hormone Oxytocin	Suckling	— stimulus

potency of individual chemical entities. Unfortunately it is necessary first to extract the oestrogens from urine, and the chemical procedures involved may lead to the inactivation of some oestrogenic substances, and also to the activation of some previously non-oestrogenic substances. Moreover, there are substances in urine, like androsterone, which, although not oestrogenic themselves, augment the action of oestrogens in certain assays, and sometimes there are also substances which inhibit the action of oestrogens. We spent a considerable amount of time investigating the biologically active oestrogens and their augmentors and inhibitors in the urine of patients with carcinoma of the breast both before and after operations, including oophorectomy, adrenalectomy, and hypophysectomy. We did not publish our results because we felt that a great deal more academic research was required first in order to elucidate these problems.

If we accept the limitations of the methods, however, we would agree with Scowen (1958) that there appears to be no correlation between the amount of residual oestrogen assayed biologically in urine and the progression or remission of metastatic carcinoma of the breast after endocrine surgery. Indeed, we have been impressed with one patient on whose urine we did a large series of investigations. It consistently contained biologically measurable amounts of oestrogens for nine months after completion of bilateral oophorectomy and adrenalectomy. During this time she had an excellent remission. Then simultaneously with the onset of a relapse the oestrogens disappeared from her urine and were never detectable again.

A method for the chemical determination of the three oestrogens—oestrone, oestradiol-17 β , and oestriol—has been

developed by Brown (1955) which is satisfactory for the concentrations found in the urine of women during the reproductive phase of life. Subsequently it was modified for use with urine of low oestrogenic concentration by Brown, Bulbrook, and Greenwood (1957a, 1957b). Using this procedure, Brown (1958) found that there was no significant difference in the excretion of these three oestrogens by women who had passed the menopause, whether they had carcinoma of the breast or not, and Bulbrook and Greenwood (1957) showed that oophorectomy and adrenalectomy or hypophysectomy (Greenwood and Bulbrook, 1957) in younger women caused a big reduction in excretion, but often failed to abolish it. No comprehensive analysis is available of the relationship between the amount of these oestrogens excreted and the remission or progression of the carcinoma. Perhaps such an analysis would be premature because of the shortcomings of the methods. They do not measure certain other known oestrogens which may be present in significant amounts in urine, like 16-epioestriol, 16 α -hydroxyoestrone, or 2-methoxyoestrone, and studies with radioactive oestrogens indicate that all the known oestrogens represent only a fraction of the total metabolites (Beer and Gallagher, 1955), but apparently they do measure other substances which are not biologically active oestrogens.

Diczfalussy, Birke, Franksson, Hellström, Hultberg, Plantin, and Westman (1958) attempted to characterize substances extracted from the urine of three patients with carcinoma of the breast after bilateral oophorectomy and adrenalectomy. They obtained two substances which behaved like oestrone and like oestradiol-17 β with Brown's procedure, but they behaved quite differently in studies of counter-current distribution and there was a gross discrepancy between the amount of each substance extracted and its biological activity. It is apparent, therefore, that, as in the case of the biological assay, a great deal more fundamental research is needed into the chemistry of the oestrogens and similar substances before the relationship between the production of oestrogens and carcinoma of the breast can be settled.

Progesterone ; 17-Ketosteroids

A considerable amount of attention has been devoted to other steroids. Progesterone, which plays such an important part in the development of the breast, cannot be measured in blood or urine as a routine procedure. Some 20% of circulating progesterone is converted into an inert and more readily soluble steroid, pregnanediol, and a satisfactory method has been developed for its determination in urine (Klopper, Michie, and Brown, 1955). Unfortunately other steroids, including adrenocortical steroids, are also partly converted into pregnanediol, but the amount excreted in urine is commonly regarded as a good reflection of the level of circulating progesterone. Pregnanediol disappears from urine after oophorectomy and adrenalectomy (Strong, Brown, Bruce, Douglas, Klopper, and Loraine, 1956), and its absence is probably a good indication of complete ablation of glandular tissue. No attempt has been made to use this procedure as an indication of hormone dependence in carcinoma of the breast.

The 17-ketosteroids have also received attention. They constitute a conglomeration of substances whose only common denominator is a ketone in position 17 of the steroid nucleus. Some of them are biologically inert, others are androgenic, and yet others have widely different endocrine activities. Measured as a group they are of little or no clinical value now that better and more specific procedures have been developed, especially for the measurement of adrenocortical function. Various methods have been developed for the subdivision of neutral 17-ketosteroids into smaller groups which can be measured separately or for the isolation of individual members of the groups.

A number of workers have applied these procedures to the urine of patients with carcinoma of the breast, but only one group has claimed to show significant differences in

excretion between patients who respond to glandular ablation and those who do not. In a preliminary report Allen, Hayward, and Merivale (1958) showed that the ratio of 11-deoxy-17-ketosteroids to 11-oxy-17-ketosteroids is reduced in patients who subsequently fail to respond to oophorectomy and adrenalectomy or to hypophysectomy. This work has been criticized by Kellie (1958) on the grounds that the method which they employed gives rise to artifacts, and certain 11-hydroxylated 17-ketosteroids are hydrated and appear in the 11-deoxy group. Moreover, Plantin, Birke, Diczfalussy, Franksson, Hellström, Hultberg, and Westman (1958), in a similar investigation, found no such differences. If the work of the group at Guy's Hospital is eventually confirmed it would be of considerable clinical value in helping to decide which patients are most suitable for endocrine surgery, and further results are awaited with interest.

Pituitary Hormones

There remains a group of pituitary hormones which play various parts in the development of the normal breast. They comprise S.T.H., M.T.H., corticotrophin, and the gonadotrophins. Various methods have been developed for the assay of S.T.H. and corticotrophin in extracts from animal pituitary glands, but none is suitable for the routine examination of blood or urine. The assay of M.T.H. in human body fluids is little better. The response of the pigeon-crop gland to injections of urinary extracts has been employed by Coppedge and Segaloff (1951) as a measure of M.T.H. Using this method, Segaloff and his co-workers claimed to show changes in the excretion of M.T.H. by patients with cancer of the breast treated with a variety of steroid hormones (Segaloff, Horwitt, Carabasi, Murison, and Schlosser, 1953; Segaloff, Carabasi, Horwitt, Schlosser, and Murison, 1954; Segaloff, Gordon, Carabasi, Horwitt, Schlosser, and Murison, 1954), but it is doubtful if the method is sensitive or reliable enough for clinical use.

Hadfield (1958a) has used the proliferation of the mammary gland of the immature male mouse as an end-point of an assay for what he terms "pituitary mammotrophic substances." The method has been criticized on the grounds that many substances can cause breast development, and there is insufficient evidence about the specificity of this assay. He has partly overcome this difficulty by using hypophysectomized weanling male mice, but very few mice are suitable for the test. He found that only two out of 36 strains examined were satisfactory, and when these two strains were used in another laboratory they were found to have lost their responsiveness (Williams, 1958). Such variation in the sensitivity of a strain to different substances is not uncommon, and sometimes presents considerable difficulty in assay work. The onus lies with the critic to repeat the work until successful. A more serious criticism is that there is insufficient evidence about the precision of the assays performed by Hadfield, but doubtless this information will be forthcoming. Meantime, Hadfield has claimed to be able to demonstrate "mammotrophic substance" in the urine of 57% of women who had passed the menopause and of all younger women during the second half of the menstrual cycle. Recently he (Hadfield, 1958b) has applied the method to the serum of five younger women and found activity in all of them. This work is potentially of such importance in the investigation of cancer of the breast that it warrants considerable effort to repeat it elsewhere.

The assay of urinary gonadotrophins is on rather firmer foundations. The majority of workers use the increase in weight of the uterus of the immature mouse as a measure of the combined effect of follicle-stimulating hormone (F.S.H.) and of luteinizing or interstitial-cell-stimulating hormone (I.C.S.H.). Loraine (1958) used this procedure to measure total gonadotrophins excreted by women with carcinoma of the breast who had passed the menopause. He claimed that those who subsequently failed to respond to treatment with stilboestrol excreted significantly more than those who responded to it. Further studies along these lines are awaited

with interest. The excretion of urinary gonadotrophins has also been employed as an indication of complete hypophysectomy. We have used the test as a semi-quantitative procedure but our interest has been more concerned with the development of assays capable of demonstrating differences in the relative concentrations of F.S.H. and I.C.S.H. These methods have not yet been applied to the problem of cancer.

Persistence of Steroids after Gland Ablation

The discovery that various steroids continue to circulate in the blood and to be excreted in the urine after ablation of the glands which secrete them has led to a reappraisal of the methods of treatment and to a reconsideration of their sources of origin. Incomplete removal of the ovaries or adrenal glands is one possible explanation for the persistence of oestrogens and certain other steroids, and the presence of accessory cortical tissue is another. It has been suggested that stimulation with corticotrophin might demonstrate their presence by causing an increased production of steroids, but it is not generally helpful, possibly because the glandular tissue is already working to its maximum capacity. The incidence of such tissue should be known from necropsy studies, but the remnants may easily be missed unless serial sections are made of large areas. Accessory adrenocortical tissue has been estimated by various workers to occur in some 20% of all subjects. Symington, Grant, O'Donnell, Carr, and Forrest (1958) reviewed the literature on this subject and failed to demonstrate such tissue in a very careful examination of their own material at necropsy. It seems to be unlikely that accessory adrenal glands are a common source of persisting steroids after adrenalectomy, and their origin must be sought elsewhere, possibly from exogenous sources.

The failure of hypophysectomy to relieve all patients with carcinoma of the breast may be due to the presence of accessory anterior pituitary tissue in the roof of the pharynx. This subject has been reviewed by Müller (1958), who found a pharyngeal pituitary consistently in all his own material at necropsy. Its functional significance is uncertain. It contains chromophobe and eosinophil cells and is known to have been the site of an eosinophilic tumour associated with acromegaly. It contains no basophil cells, which might explain the absence of urinary gonadotrophins after hypophysectomy, while S.T.H. and M.T.H. might continue to be produced by the pharyngeal remnant. Ultimately its significance must be established by the development of methods for the assay of the hormones which it produces.

In conclusion we are faced with this challenge. Empirical surgery has established the existence of hormone-dependent carcinoma, and all the biologists, chemists, and pathologists together have so far been unable to explain it.

Summary

Growth hormone acts synergistically with oestrogen to cause ductal growth, and lactogenic hormone acts synergistically with progestogen to cause lobular growth in the breast of immature rats deprived of their pituitary and steroid-producing glands. Little is known, however, of the concentrations of these hormones required for normal breast development in the human subject, but it seems likely that they all may play some part in the development of hormone-sensitive types of breast cancer.

There are several important technical factors which detract from the value of biological and chemical estimations of the various hormone concentrations in blood and urine, and, so far, no convincing correlation has been demonstrated between the remission or progression of cancer and the residual excretion of oestrogens or other steroids. The assay of growth and lactogenic hormones in body fluids is not practicable as a routine procedure at the present time.

The remarkable clinical improvement of patients with breast cancer which sometimes follows hypophysectomy or adrenalectomy and oophorectomy is still not satisfactorily explained.

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AN ANALYSIS OF 161 CASES OF CARDIAC INFARCTION WITH ABC ELECTROCARDIOGRAPHIC STUDIES AND 36 NECROPSIES*

BY

E. R. TRETHEWIE, M.D., D.Sc., M.R.A.C.P.

From the Department of Physiology, University of Melbourne and the Royal Melbourne Hospital, Australia

In the *Lancet* (1954), in a section concerning vectorcardiography and referring to the ABC display, it was stated that "satisfactory electrocardiograms have been obtained from cases of known heart disease, but confirmation from larger numbers is needed." In the present paper 161 cases of cardiac infarction observed over a period of 2-8 years by the ABC display have been studied with this end in view. Necropsies were performed on 36 cases of this series.

The standard unipolar limb and chest leads record electrical activity almost solely in the frontal (coronal) plane. The vectorcardiograph is limited with regard to the study of temporal relationships and the acceptance of a standard frame. This simple three-dimensional display, allowing a three-dimensional analysis, is not deficient in these respects. As will be seen from this survey, it detects all changes detected by the present normal leads, and in addition detects changes not demonstrated by the normal leads.

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The series of patients is classified into the following groups.

A. (i) Clinically diagnostic, standard E.C.G. diagnostic, ABC leads diagnostic: 127 cases; 32 traced deaths, 25 necropsies. (ii) Clinically diagnostic, standard E.C.G. not diagnostic, ABC leads diagnostic: 24 cases; 5 traced deaths, 5 necropsies.

B. Clinically not obvious, standard E.C.G. not diagnostic, ABC leads diagnostic: (i) fatal cases 4, 2 necropsies. (ii) survivors 2.

C. Infarct totally unexpected, ABC leads diagnostic: 1 case (necropsy positive).

D. Clinical diagnosis infarction, ABC leads negative: 1 case (necropsy negative).

E. Special instances: (i) Minor infarct patterns: 4 cases; 1 traced death, 1 necropsy. (ii) Abnormal T-wave form (also included in A): 1 case. (iii) heart block (also included in A): 17 cases; 12 traced deaths, 9 necropsies.

Method

The majority of the patients were examined personally by me, and the condition of all patients was discussed with at least one physician concerned with the management of each patient.

FIG. 1.—(a) Planar sheet (diagrammatic) of infarction AB at right-angles to YOY. Further details in text. (b) Linear infarction, C, at right-angles to A and B axis. Further details in text. (c) Four dipoles paired and orientated at 180 degrees. Further details in text. (d) Clockwise dipoles. Further details in text. (e) Direction cosines (0,0,1; 1,0,0; 0,1,0) to ABC axis. Further details in text.

E.C.G. recording was usually performed with a Both direct writing electrocardiograph and in some instances with a "cardio-scribe" direct writing machine. A continuous check was made to ensure that the recording apparatus was kept in good condition.

When patients died every endeavour was made to have a necropsy performed, though this was not always possible owing to conditions beyond our control. In some instances the freshly removed intact heart was perfused through the coronary vessels with a gelatin-barium suspension at 37° C. and 120 mm. Hg pressure and then x-rayed as described by Blumgart *et al.* (1940).

ABC electrocardiographic recording was made from the right-angled system: xiphisternum (X), manubrium