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Hormone receptors and breast cancer

Hormone deprivation may cause dramatic remission of disease in women with advanced breast cancer, and sometimes this may last for 15 years. Unfortunately only 30% of women respond in this way, so that massive efforts have been made to predict which individual will respond to treatment by hormone deprivation.

Normally an essential first step in the response of hormone-sensitive tissues is binding of the hormone to a receptor protein in or on the target cell. For steroids and other small-molecule hormones receptors have been found in the cytoplasm, while for polypeptide hormones (which penetrate the cell less easily) these seem to be located on the surface of the cell membrane. In general, hormone receptors are found only in hormone-sensitive tissues. This led Jensen[1] to suggest that the hormone-receptor content of tumours might be used as an index of their hormone responsiveness, and in rats hormone-dependent tumours have been shown to contain more receptor sites per cell than their unresponsive counterparts.[2 3]

Oestrogen receptors were first demonstrated in human breast tumours by Korenman,[4] and several techniques are now available for measuring them. Depending on menstrual status and the criteria chosen, this incidence is between 40 and 85% of human breast cancers. One American series[5] compiled data from 380 patients in eight centres, with the response to treatment classified by two external assessors. If a tumour did not contain oestrogen receptors then the chances of remission in response to endocrine treatment were only 8%, whereas if oestrogen receptors were present 43-60% of patients responded favourably to endocrine treatment, but treatment with anti-oestrogens achieved higher response rates (16%) in patients in whom receptors were not present. Moreover, the presence of oestrogen receptors is now known to correlate not only with the success of antioestrogens but also with that of other kinds of hormonal treatment. Thus oestrogen receptors may be only one type of marker for a generalised tendency to respond to this form of treatment.

The presence of oestrogen receptors in malignant cells is evidence that at least a part of the hormonal control mechanism remains intact. Nevertheless, in 40-60% of patients the tumours appear to have oestrogen receptors but do not respond to endocrine treatment. Probably here some part of the hormonal control mechanism other than the cytoplasmic binding is not functioning, and this is also true for some animal tumours.[6 7] One explanation could be absence of the x-protein believed[8] to be essential for the hormone-receptor complex to interact with the nucleus, or there could be autonomy of RNA-polymerase normally[9] dependent on such interaction.

An ideal marker of endocrine responsiveness in a tumour would be a measurable product of hormone action rather than just the initial binding step, and several tissue culture methods are being explored.[10 12] In oestrogen target tissues the synthesis of progesterone receptors may depend on the intact response to oestrogen,[13] and the presence of progesterone receptors may become such a marker for functional oestrogen receptors in human breast tumours. The advent of a synthetic analogue, R5020, which does not bind significantly to cortisol sites enabled progesterone receptors to be detected in 57% of breast cancers (together with oestrogen receptors in 49%).[14] The clinical role of the presence of both receptors has yet to be evaluated, but already the incidence seems too high to predict the 20-40% of patients who will respond to treatment.

Androgens also may promote human breast cancers,[15] and androgen receptors have been found in animal and human breast tumours,[16–18] though studies have been based on too few patients for any proper assessment of their clinical value. In one trial it seemed possible that the 14% of the patients with breast cancer who responded to high-dose oestrogen (an antiandrogen) might be a different group to the 31% who responded to an antioestrogen. As no cross-over study was made[19] this remains an open question; these results emphasise the need for the full receptor status to be determined among patients entered into trials of antihormonal treatments.

The main peptide hormone implicated in promoting the growth of breast tumours is thought to be prolactin. Prolactin receptors have been found in the membrane fractions of various rodent mammary tumours, and the degree of prolactin-binding is correlated with the growth response of the tumour to exogenous prolactin.[20 21] Growth hormone[22] and human placental lactogen[23] have now been implicated in promoting human breast cancers. The binding of prolactin, growth hormone, and placental lactogen to frozen sections of human breast tumours has been shown using an immunoenzyme bridge method,[24] and clinical evaluation of this new approach is awaited.

These evaluations have shown the need to monitor serum levels of prolactin and growth hormone and also to use thyrotrophin releasing hormone and stress tests after hypophysectomy.[25] Residual growth hormone may be found in 30% of cases and residual prolactin in 70%, so that the disappointingly low figure of 40% of regressions after hypo-

physectomy should not be allowed to bias future practice. If the presence of these hormones can be abolished by newer methods then the proportion of regressions might be improved, especially if a simple reliable means can be found for identifying patients whose tumours are dependent on prolactin and growth hormone.

In conclusion, then, receptors may now be detected (at least presumptively) in human breast, prostatic, endometrial, and other cancers, and these preferentially bind oestrogen, androgen, progesterone analogue, prolactin, growth hormone, or placental lactogen. Their possible permutations and interrelationships emphasise the heterogeneity of human cancers, and breast cancer in particular—making it clear that there can be no single best treatment. Even though quadruple cytotoxics may yield the largest immediate number of remissions in breast cancer, most of these are short-lived, and after relapse there may be less chance for antihormonal treatments.[10] The most hopeful prospect is that work may determine criteria for study of the actual breast cancer of a given patient—before it all gets into formalin—to choose the best treatment for that patient at that time.

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Chronic urticaria

Estimates of the incidence of urticaria differ quite widely,[1] but all agree that it is common. In the more dramatic, acute form of urticaria there is often a clear allergic cause, and such cases may understandably lead doctors to equate urticaria in general with allergy. Yet there is no association between chronic, as distinct from acute, urticaria and a personal or family history of atopic disorders,[2] and the competent and critical investigation of patients with chronic urticaria rarely establishes an allergic cause. In one such investigation[3] 100 patients with chronic urticaria were admitted to hospital for detailed study: food allergy was considered to be responsible for the urticaria in one patient but in the remaining 99 no unequivocal aetiological factors were discovered. Possibly chronic urticaria may be caused by an abnormality (or more probably any one of several abnormalities) in the pharmacological mediators of weal formation, but the precise nature of these postulated abnormalities is still speculative.[4]

The management of the patient with chronic urticaria is always difficult, and one American dermatologist is reported to have said that he would prefer to have a lion in his consulting room. The observation that aspirin releases histamine in patients with urticaria pigmentosa[5] was therefore a useful advance which has led to a practical and fruitful approach to this frustrating problem. Moore-Robinson and Warin[6] later showed that a provocative test dose of aspirin caused a definite aggravation of the urticaria in 22% of patients. The number of substances which, like aspirin, appear to enhance the urticarial reaction is now considerable.[7 8] They include tartrazine and other azo dyes, which are used to colour many foods and some drug tablets, and sodium benzoate and 4-hydroxybenzoic acid, used as preservatives in pickles, sauces, instant coffee, and other foods and beverages. Drugs such as indomethacin may have a similar action, and so may penicillin, though it usually causes urticaria by an allergic mechanism.[1] The yeast candida in the gastrointestinal tract and brewer's yeast may also cause urticaria by an immunological mechanism, but they may also non-specifically enhance the urticarial weal. These observations, abundantly confirmed by much published and unpublished experience, have enabled dermatologists to devise several screening procedures for urticaria. While they do not establish the "cause" of chronic urticaria they do allow the elimination of exacerbating factors with considerable benefit to the patient.

Recently Warin and Smith[9] reported an excellent example of this type of procedure. All of their 111 patients had had urticaria for at least two months. They were each given a series of identical capsules containing various doses of one of the following substances: tartrazine, sodium benzoate, 4-hydroxybenzoic acid, tyrosine, penicillin, aspirin, brewer's yeast, candida, or lactose (as a control). One numbered capsule was taken each day, and any reactions were recorded by the patient on a chart. If the chart suggested a reaction to a particular substance all the capsules were administered again, but in a different order. If the second chart incriminated the same substance as the first, then the test was recorded as positive. After a pilot study the candida was omitted since reactions to it paralleled those to brewer's yeast, which is much easier to obtain and to handle. Exacerbations of the urticaria were induced by one or more of the test substances in 66 of the patients, with aspirin well at the top of the list.

Each patient was given an appropriate diet sheet instructing her how to reduce to a minimum her intake of the substance or substances to which she had reacted. Warin and Smith followed up 47 of the patients, and 35 of them were cured or considerably improved. They acknowledged the spontaneous cure that may occur in chronic urticaria and they therefore interpreted their findings cautiously. But their conclusion that the screening procedure and the diet were "well worthwhile" will be endorsed by other dermatologists who have made use of similar routines.

Some of these offending substances are used so extensively by the food industry that it is far from easy for a busy housewife to provide herself with the prescribed diet. It is, for example,