to be the protection of animals in laboratories rather than the regulation of experiments. Furthermore, the scope of the word experiment is likely to extend beyond its historic limits; and inevitably future annual returns will then show more "experiments." This change should be welcomed, for inclusive figures are preferable to apparently reassuring ones which do not represent all the facts.

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Tumour markers in breast cancer

Tumour markers are already used in the routine management of some types of cancer. Measuring the serum acid phosphatase concentration aids the diagnosis of prostatic carcinoma, and estimating monoclonal globulin is valuable both in diagnosis and in monitoring treatment in patients with myeloma. More sensitive markers, such as calcitonin in thyroid medullary carcinoma and human chorionic gonadotrophin (HCG) in choriocarcinoma, can be used to identify a tumour before it becomes detectable by other means.[1 2]

As yet, however, no effective diagnostic marker has been found for primary breast cancer; none tested has both the sensitivity and the specificity required. Even so, less sensitive markers would be of clinical value in metastatic disease, firstly, in selecting patients for additional treatment after mastectomy and, secondly, in the early identification of the failure or success of treatment. Patients might then be spared inappropriate or ineffective treatment, and new regimens could be evaluated more rapidly and with greater accuracy.

While there is no ideal single marker for breast cancer, many patients do have raised urinary or serum concentrations of various substances which appear to be related to tumour stage. This presents the possibility of using a combination of markers, either in a multivariate analysis or as a screening procedure to pick out the best marker for follow-up in that patient. The putative markers most frequently studied are milk proteins (casein[3] or lactalbumin[4]); known products of other tumours (carcinoembryonic antigen (CEA), human chorionic gonadotrophin (HCG), or calcitonin); acute-phase proteins (haptoglobin or C-reactive protein); and serum enzymes (such as alkaline phosphatase).

Tormey *et al*[5] measured CEA, HCG, and a nucleoside: they found one or more of these abnormal in 97% of patients with advanced disease and in 67% of patients with diseased nodes after mastectomy. Franchimont *et al*[6] described one or more abnormalities in 69% of patients with local and in 89% of those with advanced disease on the basis of serum assays for CEA, casein, HCG, and HCGβ. The measurement of 19 markers, including acute-phase proteins and possible tumour products, turned up abnormalities in all 17 patients with metastatic disease but in only two of nine patients with local breast cancer.[7]

Though impressive, these cumulative abnormalities should be interpreted with caution for several reasons. Firstly, the more substances measured the more false-positive results will occur, unless the normal ranges are expanded. Secondly, even in advanced disease, many of the abnormalities are only just above the normal range, suggesting that they are unlikely to be sensitive guides to the amount of tumour. Thirdly, the abnormalities reported with some of the markers vary greatly among authors and even among different publications from the same authors. These apparent discrepancies cannot be explained by differences in the patients studied and are in part due to assay differences. For example, a raised serum calcitonin concentration was reported in all of eight patients studied by one group,[8] but later the same authors reported raised values in only two of 17 patients.[7] Abnormal casein concentrations were described in 80% of patients with metastatic disease[3] but later in only 44%, despite a reported increase in assay sensitivity. Others have found raised casein concentrations in only 19% of the patients studied[9] or even no more often than in controls.[10] The fourth factor is that the value of studying acute-phase proteins is likely to be limited because they can be affected by treatment which alters the host's immune responsiveness, irrespective of the effects on the amount of tumour. Biochemical changes within the normal range[11] are difficult to interpret unless the physiological variation is known.

The results of CEA assays have proved more consistent among authors, but finding a marker that is commonly abnormal is only the first step in defining its clinical value. Well-designed longitudinal studies showing that marker concentrations alter appropriately in relation to progression or regression of tumour have been reported only for CEA[12] and HCG.[13] There are no satisfactory reports of serial measurements after mastectomy to determine the "lead-in time" (the period by which a marker abnormality precedes clinical evidence of recurrence).

We have too little information about any of the tumour markers to justify their use in determining treatment at any stage. Possibly in advanced metastatic disease the effects of treatment could be monitored more precisely by a combination of markers, but as treatment is mainly palliative their use would be unlikely to result in any direct improvement in morbidity or mortality. In local breast cancer we need new and more sensitive tumour markers—probably tumour products—if we are to identify patients with minimal residual disease accurately. Nevertheless the present markers may help to identify patients with a higher probability of having residual disease[13] than those selected by the degree of lymph node disease alone.

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