CLINICAL VALUE OF PREDICTIVE TESTS FOR ADVANCED BREAST CANCER. E. ENGELSMA. Netherlands Cancer Institute, Amsterdam.

Endocrine therapy is known to be of value to some patients with advanced breast cancer. The patients who experience remission after endocrine therapy are said to have hormone dependent tumours. The survival of patients with hormone dependent tumours is better than of those with non-responsive tumours. With different endocrine measures, remissions can be brought about in about 30% of the patients. The quality of the remissions obtained by hormone additive therapy: oestrogens, androgens, antioestrogens and corticosteroids can be quite good, but as a rule the quality of the remissions seen after the ablative procedures like oophorectomy, adrenalectomy and hypophysectomy is better.

However, to achieve the 30% of good remissions, the 70% non-responders have to pay a heavy price, especially if the therapy is adrenalectomy. The average survival of the non-responders to adrenalectomy is short.

Any test to predict the response to endocrine therapy would be most welcome. Several techniques have been investigated: measuring the symptom-free interval has some value; with the famous discriminant function of Bulbrook and Hayward some selection is possible; the meaning of the measurement of steroid sulphate synthesis in breast cancer tissue is still unclear; the behaviour of radioactive phosphorus in the tumour in vivo can possibly give some information but is not a practical test. The short-term cultures of breast cancer tissue in different endocrine environments might be of practical value. Much work has been done by Braunsberg’s group to show that there is a correlation between the uptake of radio-labelled oestradiol by the tumour in vitro and the response to endocrine therapy, but this method cannot be made into a routine test.

It seems that with the determination of oestrogen receptors in the cancer tissue in vitro, a test has come to hand which can be used as a routine and has a good predictive value. The work of Jensen, Gorski, Korenman, Jungblut, Wagner, Terenius and others has made this possible. Jensen demonstrated a good correlation between the presence of receptors in breast cancer tissue and a favourable response to subsequent adrenalectomy, Maass showed that the correlation was also valid for other endocrine treatments.

In our Institute the study of oestrogen receptors in breast cancer metastases was facilitated by the circumstances that our staff work together as a team and that all the services needed are found under the same roof: surgery, internal medicine, pathology and biochemical laboratories. The advanced breast cancer cases were usually treated according to clinical trial protocols of the EORTC Breast Cancer Group; the receptor determinations were done initially by a charcoal absorption technique; after the 1972-EORTC Workshop on Standards for the assessment of oestrogen receptors the agar gel-electrophoresis technique was adopted, by which androgen receptors can also be determined. Only a few patients in whom the primary tumour was studied have developed metastases so far, but the advanced cases have had different types of endocrine treatment: oophorectomy, oestrogens, antioestrogens, androgens. The correlation between favourable response and presence of receptor is strong.

In the EORTC Breast Cancer Group comparable results were achieved by Maass and Trams in Hamburg, who found 20 remissions in 32 receptor positive cases and 2 remissions in 37 receptor negative cases. Heuson and Leclerq in Brussels noted 6 remissions in 18 receptor positive cases and 1 remission in 12 receptor negative cases. In all series the correlation seemed less strong for nafoxidine (antioestrogen) treatment. In our own material there is a suggestion that nafoxidine as the first treatment can produce remissions, but prevents a second therapy with oestrogens from being effective. After a successful first therapy with oestrogens, nafoxidine could produce a second remission in several patients and so it might be better to use nafoxidine in the treatment of advanced breast cancer only after oestrogens have been timed. In 3 patients with receptor negative tumours who had subjective remissions with oestrogens or androgens, a new tumour biopsy, taken after the therapy was stopped, contained receptors. This finding suggests that oestrogen receptors can be induced by hormone treatment. Oestrogen receptor determinations seem to be useful in the prediction of response to endocrine treatment; it is certainly necessary to achieve more insight into the dynamics of the
receptor–hormone interaction and its biological significance.

**PREDICTIVE VALUE OF ACID PHOSPHATASE.** B. MORGAN. Department of Chemical Pathology, University of Leeds.

There is increasing interest in the use of clinical and biochemical data to assess the probability that a patient has, or will develop, a particular state. The complexity of these techniques arises in part because they are based on many variables measured in each individual. Yet the aims of these techniques are identical with the aims of making a single measurement in each individual. It is these aims which will be discussed here in relation to a single variable, namely the serum acid phosphatase activity, and a single clinical condition, namely carcinoma of the prostate.

The *ideal situation* would have been as follows: (1) Two groups were defined which were comparable in all ways except that one group had carcinoma of the prostate gland (CA) and the other did not (N); (2) There was a measurement (*acid phosphatase*) which was simpler than the techniques used to separate the initial groups and which had different values in the groups CA and N; (3) There was no overlap in the values of X in the groups CA and N; (4) There was no other condition which could be confused with carcinoma of the prostate.

The real life situation is of course far from this ideal. One fundamental difference is that there is no complete separation of the values of serum acid phosphatase (AP) in the two groups (N and CA). Various changes in technique have been suggested in order to diminish this overlap of AP between the groups. These changes are largely aimed at improving organ specificity by the choice of substrate and the addition of isoenzyme inhibitors (Bodansky, *Clin. Chem.*, 1972, 15, 43; Schwartz, *Clin. Chem.*, 1973, 19, 10).

While these attempts will no doubt continue, it seems reasonable to conclude that in this clinical situation, as in so many others, a single measurement will not completely discriminate between the groups and that overlap of the results will remain.

What is so commonly done in practice is to define a value (the upper limit of normal) to assume that values above this will not occur in healthy persons. The finding of a high value then "indicates" the presence of the disorder. This approach is an attempt to make the situation like the ideal one with complete discrimination.

However, this approach makes no use of the information in the absolute value of the measurement. Thus, the higher the value of AP, the greater the probability of carcinoma of the prostate. This probability is rarely formally defined for a single variable although it is now part of some complex statistical analyses involving several variables (Hartz, *Clin. Chem.*, 1973, 19, 113). This probability function must also take into account the relative prevalence (probabilities) of the disorders or states which are being discriminated.

**MULTIPARAMETRIC TESTS IN THE STUDY OF GASTROINTESTINAL NEOPLASMS.** E. H. COOPER. Department of Cancer Research, University of Leeds.

Several forms of cancer can be conveniently staged into a local growth, extension into local nodes, direct spread beyond the organ of origin and distant metastases. This sequence will have reached various stages when the patient first presents and after a variable time interval following the excision of the primary tumour local recurrences or distant metastases may develop. A team of laboratory workers and clinicians in the Leeds Region and at the Chester Beatty Institute, London has been examining the way in which laboratory tests may aid the diagnosis in gastrointestinal cancers, in particular, colorectal cancer. This was chosen partly in view of our participation in the MRC trial on the evaluation of carcino-embryonic antigen (CEA) and partly as the evolution of colorectal cancer follows reasonably well-defined patterns. It soon became apparent that apart from being able to distinguish metastatic colorectal cancer involving the liver from various types of hepatitis and cirrhosis, CEA alone was unable to discriminate the various stages of evolution of colorectal cancer. As the liver is the main site of distant metastasis the contributions of serum enzyme, known to be elevated in hepatic metastases, to a discriminant function have been examined. Gammaglutamyl transpeptidase, leucine aminopeptidase and alkaline phosphatase