Trials recently established by the International Union Against Cancer is a welcome move.⁷⁵

Quite correctly most of the clinical trials in progress are comparing methods which include treatment of the whole breast and the regional lymph nodes. We are now entering an era when serious consideration is being given to the setting up of trials in which one group of patients will have no primary treatment to the regional nodes even if they are thought to be involved clinically. Participation in such an investigation must to a certain extent be a matter of individual conviction and conscience, and my own personal opinion is that such a trial would be premature. We cannot ignore the fact

that many women with early involvement of the axillary lymph nodes are cured of the disease only by primary treatment to the whole of the diseased region. Treatment of the patient in this category must be based on the expectation of cure. Equally we have to concede that to this day we remain undecided over the methods of treating the *whole* region and perhaps this should be settled before unorthodox methods are introduced.

The real hope for the immediate future must lie in our ability to diagnose cancer of the breast much earlier than hitherto, so that we may treat an ever increasing proportion of patients with genuinely localized disease.

Treatment of the Advanced Disease

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British Medical Journal, 1970, 2, 469–471

There are now many measures available to treat advanced breast cancer. Nevertheless, only if the right therapies are selected and given in the proper sequence can they be used to the best advantage. At this stage of the disease a cure is impossible at present. Hence the principal aim in the patient's management must be to improve by the simplest means possible the quality of what life remains to her. Such treatment may prolong survival but this is not necessarily the most important aim. In essence, therefore, treatment should be symptomatic, aiming by local or general measures to relieve distressing symptoms and, by sensible anticipation, to postpone the development of further symptoms.

While metastases are still localized, radiotherapy or local surgery may suffice to keep the disease under control. Only when the disease has become more widespread and the use of local treatments has been exhausted should general measures be considered.

Castration

Castration was the first therapy shown to affect the progress of advanced breast cancer, and it is still considered the treatment of choice in premenopausal women. The method used is probably unimportant,^{76–78} though oophorectomy has a more immediate effect than ovarian irradiation.⁷⁹ The remission rate depends on the criteria of a successful response. When only objective evidence of response is accepted probably 20 to 25% of patients are helped, but in many this remission is short lived.

There has been much debate on the value of castration in postmenopausal women. From the results of a trial of prophylactic castration R. Nissen-Meyer⁷⁸ inferred that this could be of value in women up to the age of 70. On the other hand, it is known that removing the ovaries in postmenopausal women has no effect on oestrogen production.⁸⁰ Hence if any benefit comes from interference with oestrogen production it is difficult to see how castration in postmenopausal women with breast cancer can have any effect on the tumour. Also J. J. Barlow and his colleagues⁸⁰ were able to find only 16 authenticated cases in which postmenopausal women with breast cancer have responded to castration, and similarly A. A. Fracchia and his co-workers⁸¹ reported that only three of their 85 postmenopausal breast-cancer patients responded to oophorectomy—and in each case the patient was within one year of the menopause.

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Androgens and Oestrogens

Most recent work on androgens and oestrogens has concentrated on trying to produce compounds giving a higher remission rate than those in general use.⁸² Most of the work has been done on androgens, but no new compounds have been found which give a consistently higher response rate than the reference compound—usually testosterone propionate. Nevertheless, this research has introduced androgens with fewer virilizing effects, a development which has certainly made the side-effects of this treatment less unpleasant.^{83 84}

Probably no androgen or oestrogen will be found which will have a significantly greater effect on breast cancer than those in use today. The remission rate achieved at present appears to reflect the proportion of tumours in a population that are responsive to additive hormone therapy, and no modification of the androgen or oestrogen molecule will alter this. At present the usual practice is to administer androgens to women who are up to five years' postmenopausal, and oestrogens from then onwards. The remission rates from the two compounds increase with advancing age.^{82 85 86}

Progestogens

Though progestogens undoubtedly have an effect on breast cancer their precise role in treating the advanced disease has not yet been clarified. Few properly controlled clinical trials have been carried out, but the available information indicates that there is little difference in the relative efficiency of progestogens, androgens, or oestrogens.⁸⁷ The principal advantage of progestogens is their relative lack of side-effects. Two preliminary reports that progestogens can induce a remission in patients failing to respond to adrenalectomy or hypophysectomy are of great interest.^{88 89}

Corticosteroids

It is now generally accepted that corticosteroids can cause metastatic deposits from breast cancer to regress. Whether this results from a local effect on the tumour or whether it is mediated through the action of the corticosteroids on the adrenal glands is not known, though probably the latter effect predominates.⁹⁰ Certainly in many cases corticosteroids cause adrenal atrophy, but the degree of this is less than that after hypophysectomy.⁹¹ Nevertheless, corticosteroids are no substitute for major ablation;^{92 93} the remission rate is probably less and the duration of response shorter. These compounds are now used mostly for patients who have not

responded to hormone therapy and who are either too ill or too old to be subjected to adrenalectomy or hypophysectomy.

Adrenalectomy and Hypophysectomy

These operations give the highest rate and the longest duration of remission of any of the treatments available for the advanced disease. Again, the remission rate depends on the criteria of response, but is probably two to three times that of castration or hormone therapy. Conventionally these operations should be used only as a last resort, and all forms of simpler therapy (surgery, radiotherapy, androgens, or oestrogens) should be tried first. Only when these have failed should major ablation be undertaken. Recent tests of this practice have shown it to be sound. Three trials have been carried out in which patients with advanced breast cancer have been treated in two ways—either by conventional measures followed by ablative surgery or by immediate adrenalectomy or pituitary ablation without a previous trial of hormone therapy. The survival and remission experience of both groups of the patients were almost identical and in each case it was concluded nothing could be gained by early operation.⁹³⁻⁹⁵

The choice of operation in a particular patient is determined largely by the facilities available. In ideal conditions surgical hypophysectomy by the transfrontal route gives a slightly higher remission rate than adrenalectomy.⁹⁶ Nevertheless, if expert neurosurgical facilities are not available the morbidity rate is such that adrenalectomy must be preferred.⁹⁷ Transphenoidal hypophysectomy also has a high morbidity rate and in many cases it may be uncertain whether the entire gland has been removed. Even so, from the patient's point of view, transphenoidal hypophysectomy is easier to tolerate than the transfrontal operation. Destruction of the pituitary by an implant of ⁹⁰Yttrium also gives a good remission rate but probably not as high as that obtained by adrenalectomy,⁹⁸ because of the minor side-effects of the procedure, Yttrium implantation is ideally suited for the very ill patient.

Cytotoxins

Both cyclophosphamide and 5-fluorouracil have an effect on breast cancer. The remission rate is high (some improvement in the lesions being expected in over half the patients) but the duration of response is short. Cytotoxins are certainly no substitute for endocrine ablation but they can be useful when this fails and particularly in treating localized offensive

lesions. Cyclophosphamide, the compound most frequently used in Britain, can effect the most dramatic improvement in ulcerating and fungating skin lesions. The drug is particularly useful because it can be given by mouth, and the patient can be managed without admission to hospital.

Tests of Prediction

Since adrenalectomy and hypophysectomy were introduced for treating advanced breast cancer a method of predicting those patients most likely to respond has been badly needed. Early attempts at assessing prognosis by using tumour differentiation⁹⁹ or levels of oestrogen excretion¹⁰⁰⁻¹⁰² did not prove successful. Some consider a successful response to ovarian ablation to be a good prognostic sign,^{103 104} but this can be a useful guide in only relatively few cases.^{105 106}

Measurements of the levels of androgens and corticosteroids in the urine of women before ablation gives some indication of the likely response. Combined either as a discriminant function,¹⁰⁷ or as a ratio,¹⁰⁸ the levels of these hormones can be used to identify a group of patients with nearly twice the normal response rate. If certain clinical features such as the free period (those whose disease recurs within two years of mastectomy respond badly) and the menopausal state (a remission is unlikely in those women who are within six years of the menopause) are also taken into account, a further group of patients can be identified whose remission rate from subsequent adrenalectomy or hypophysectomy will be less than 5%.¹⁰⁹

Other methods of prediction are also being investigated and are giving promising results. R. E. Wilson and F. D. Moore¹¹⁰ have obtained good results using a discriminant function based on the adrenal response to stimulation by corticotrophin. T. L. Dao¹¹¹ has reported encouraging preliminary results from a method based on measuring the steroid sulphokinase activity of tumour tissue.

Improvement in the future management of patients with advanced breast cancer is unlikely to come from new methods of treatment. Radiotherapy or local surgery seem unlikely to accomplish much more than they do at present, and no hormone more effective than those in current use is likely to be produced; certainly, no further ablative procedures can be envisaged. Nevertheless, more precise prediction of the response of patients to present treatments should be possible—probably by combining hormone assays and studies of tumour behaviour both in vivo and in vitro. Only by this means, can an individual plan of therapy be chosen for each patient which will make the best use of the treatments available.

REFERENCES

- Gershon-Cohen, J., *Postgraduate Medicine*, 1969, **45**, 84.
- Strax, P., Shapiro, S., and Venet, L., in *Prognostic Factors in Breast Cancer*, ed. A. P. M. Forrest and P. B. Kunkler, p. 242. Edinburgh, Livingstone, 1968.
- Bloom, H. J. G., *British Medical Journal*, 1965, **19**, 278.
- Forrest, A. P. M., and Gravelle, I. H., *Practitioner*, 1969, **203**, 137.
- Strax, P., and Oppenheim, A., *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine*, 1968, **102**, 941.
- Gravelle, I. H., *Odelca Mirror*, 1969, **8**, 10.
- Roach, J. F., and Hilleboe, H. E., *Journal of the American Medical Association*, 1955, **157**, 899.
- Ruzicka, F. F., Kaufman, L., Shapiro, G., Perez, J. V., and Grossi, R. E., *Radiology*, 1965, **85**, 260.
- Wolfe, J. N., *Cancer (Philadelphia)*, 1969, **24**, 1222.
- Stewart, H. J., Gravelle, I. H., and ApSimon, H. T., *British Journal of Surgery*, 1969, **56**, 341.
- Furnival, I., Gravelle, I. H., Stewart, H. J., Weddell, J., Evans, K. T., and Forrest, A. P. M. In preparation.
- Williams, K. L., Williams, F. J. L., and Handley, R. S., *Lancet*, 1961, **2**, 1378.
- Lilienfeld, A. M., et al., *Cancer (Philadelphia)*, 1969, **24**, 1206.
- Shapiro, S., Strax, P., and Venet, L., *Journal of the American Medical Association*, 1966, **195**, 731.
- Strax, P., Venet, L., Shapiro, S., Gross, S., and Venet, W., *Journal of the American Medical Association*, 1970, **210**, 433.
- Venet, L., Strax, P., Venet, W., and Shapiro, S., *Cancer (Philadelphia)*, 1969, **24**, 1187.
- Barnes, S., et al., *Lancet*, 1968, **1**, 1417.
- Stevens, G. M., and Weigen, J. F., *Cancer (Philadelphia)*, 1966, **19**, 51.
- Lowe, C. R., in *Screening in Medical Care*, ed. T. McKeown, A. L. Cochrane and C. R. Lowe, p. 33. London, Oxford University Press for the Nuffield Provincial Hospitals Trust, 1968.
- Egan, R. L., *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine*, 1963, **90**, 356.
- Clark, R. L., et al., *American Journal of Surgery*, 1965, **109**, 127.
- Hessler, C., and Gershon-Cohen, J., *Acta Radiologica (Diagnosis)*, 1965, **3**, 249.
- Friedman, A. K., et al., *Radiology*, 1966, **86**, 886.
- Wallace, J. D., and Dodd, G. D., *Radiology*, 1968, **91**, 679.
- Isard, H. J., Ostrum, B. J., and Shilo, R., *Surgery, Gynecology and Obstetrics*, 1969, **128**, 1289.
- Pedersen, E., *Proceedings of the Royal Society of Medicine*, 1967, **59**, 1189.
- Witten, D. M., and Thurber, D. L., *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine*, 1964, **92**, 14.
- Wolfe, J. N., *Radiology*, 1965, **84**, 703.
- Griesbach, W. A., and Eads, W. S., *Cancer (Philadelphia)*, 1966, **19**, 1548.

- 30 Irvine, R. W., and James, W. B., *Scottish Medical Journal*, 1969, **14**, 405.
- 31 Hoffman, R. L., *American Journal of Obstetrics and Gynecology*, 1967, **98**, 681.
- 32 Hitchcock, C. R., Hickok, D. F., Soucheray, J., Moulton, T., and Baker, R. C., *Journal of the American Medical Association*, 1968, **204**, 419.
- 33 Nohrman, B. A., *Acta Radiologica*, 1949, Supplement No. 77, p. 55.
- 34 Bloom, H. J. G., Richardson, W. W., and Harries, E. J., *British Medical Journal*, 1962, **2**, 213.
- 35 Donegan, W. L., in *Cancer of the Breast*, ed. J. S. Spratt and W. L. Donegan, p. 118. Philadelphia, Saunders, 1967.
- 36 Halsted, W. S., *Johns Hopkins Hospital Reports*, 1890, **2**, 255.
- 37 Halsted, W. S., *Annals of Surgery*, 1894, **20**, 497.
- 38 Meyer, W., *New York Medical Records*, 1894, **46**, 746.
- 39 Adair, F. E., *Proceedings of the Royal Society of Medicine*, 1960, **53**, 895.
- 40 Keynes, G., *British Medical Journal*, 1937, **2**, 643.
- 41 Williams, I. G., Murley, R. S., and Curwen, M. P., *British Medical Journal*, 1953, **2**, 787.
- 42 McWhirter, R., *British Journal of Radiology*, 1955, **28**, 128.
- 43 Patey, D. H., and Dyson, W. H., *British Journal of Cancer*, 1948, **2**, 7.
- 44 Handley, R. S., *British Journal of Surgery*, 1964, **51**, 206.
- 45 Wangenstein, O. H., *Annals of Surgery*, 1949, **130**, 315.
- 46 Urban, J. A., and Baker, H. W., *Cancer*, 1952, **5**, 992.
- 47 Andreassen, M., Dahl-Iversen, E., and Sørensen, B., *Lancet*, 1954, **1**, 176.
- 48 Veronesi, U., *Acta Unio Internationalis Contra Cancrum*, 1963, **19**, 1560.
- 49 Gordon-Taylor, Sir G., *Proceedings of the Royal Society of Medicine*, 1948, **41**, 118.
- 50 Porritt, Sir A., *British Journal of Surgery*, 1964, **51**, 214.
- 51 Crile, G., jun., *Surgery, Gynecology and Obstetrics*, 1965, **120**, 975.
- 52 Bond, W. H., in *The Treatment of Carcinoma of the Breast*, ed. A. S. Jarrett, p. 24. Maidenhead, Syntex Pharmaceuticals, 1967.
- 53 Edlstein, G. J. A., *British Journal of Hospital Medicine*, 1969, **2**, 1861.
- 54 Brinkley, D., and Haybittle, J. L., *British Journal of Radiology*, 1968, **41**, 215.
- 55 Gibb, R., *British Journal of Surgery*, 1969, **56**, 791.
- 56 Fairley, G. H., *British Medical Journal*, 1969, **2**, 467.
- 57 Mathé, G., *British Medical Journal*, 1969, **4**, 7.
- 58 Hamlin, I. M. E., *British Journal of Cancer*, 1968, **22**, 383.
- 59 Galasko, C. S. B., *British Journal of Surgery*, 1969, **56**, 757.
- 60 Pickren, J. W., *Proceedings of the New York State Association of Public Health Laboratories*, 1958, **38**, 31.
- 61 Harmer, M., in *Cancer*, ed. R. W. Raven, Vol. 4, p. 1. London, Butterworths, 1958.
- 62 Denoix, P., and the Committee on T.N.M. Classification, T.N.M. Classification of Malignant Tumours. Geneva, Unio Internationalis Contra Cancrum, 1968.
- 63 Burn, J. I., *British Journal of Surgery*, 1969, **56**, 786.
- 64 Forrest, A. P. M., and Kunkler, P. B., *Hospital Medicine*, 1968, **2**, 398.
- 65 Hayward, J. L., *British Journal of Surgery*, 1969, **56**, 794.
- 66 Forrest, A. P. M., *British Journal of Surgery*, 1969, **56**, 782.
- 67 Harnett, W. L., *British Journal of Cancer*, 1948, **2**, 212.
- 68 Atkins, H. J. B., *Proceedings of the Royal Society of Medicine*, 1960, **53**, 901.
- 69 Easson, E. C., in *Prognostic Factors in Breast Cancer*, ed. A. P. M. Forrest and P. B. Kunkler, p. 118. Edinburgh, Livingstone, 1968.
- 70 Brinkley, D., and Haybittle, J. L., *Lancet*, 1966, **2**, 291.
- 71 Truscott, B. McN., *British Journal of Surgery*, 1969, **56**, 789.
- 72 Kaac, S., and Johansen, H., in *Prognostic Factors in Breast Cancer*, ed. A. P. M. Forrest and P. B. Kunkler, p. 93. Edinburgh, Livingstone, 1968.
- 73 Handley, R. S., *Cancer*, 1969, **24**, 1270.
- 74 Deeley, T. J., *Methods of Information in Medicine*, 1966, **5**, 100.
- 75 Flamant, R., *International Journal of Cancer*, 1969, **4**, 891.
- 76 Diczfalussy, E., Notter, G., Edsmyr, F., and Westman, A., *Journal of Clinical Endocrinology and Metabolism*, 1959, **19**, 1230.
- 77 Nissen-Meyer, R., and Sanner, T., *Acta Endocrinologica*, 1963, **44**, 334.
- 78 Nissen-Meyer, R., *Acta Radiologica*, 1965, Suppl. No. 249.
- 79 Block, G. E., Vial, A. B., and Pullen, F. W., *Surgery*, 1958, **43**, 415.
- 80 Barlow, J. J., Emerson, K., jun., and Saxena, B. N., *New England Journal of Medicine*, 1969, **280**, 633.
- 81 Fracchia, A. A., Farrow, J. H., DePalo, A. J., Connolly, D. P., and Huvos, A. G., *Surgery, Gynecology, and Obstetrics*, 1969, **128**, 1226.
- 82 Co-operative Breast Cancer Group, *Cancer Chemotherapy Reports*, 1964, **41**, Suppl. No. 1.
- 83 Segaloff, A., Weeth, J. B., Meyer, K. K., Rongone, E. L., and Cunningham, M. E. G., *Cancer*, 1962, **15**, 633.
- 84 Cantino, T. J., and Gordan, G. S., *Cancer (Philadelphia)*, 1967, **20**, 458.
- 85 Hayward, J. L., *Guy's Hospital Reports*, 1957, **106**, 254.
- 86 Council on Drugs, Subcommittee on Breast and Genital Cancer, *Journal of the American Medical Association*, 1960, **172**, 1271.
- 87 Co-operative Breast Cancer Group, *Cancer Chemotherapy Reports*, 1961, **11**, 109.
- 88 Kennedy, B. J., *Cancer (Philadelphia)*, 1965, **18**, 1551.
- 89 Landau, R. L., in *Major Endocrine Surgery for the Treatment of Cancer of the Breast in Advanced Stages*, ed. M. Dargent and C. I. Romieu, p. 263. Lyon, Simep Edn., 1967.
- 90 Nissen-Meyer, R., and Sverdrup, A., *Memoirs of the Society of Endocrinology*, 1961, **10**, 156.
- 91 Jantet, G., Crocker, D. W., Shiraki, M., and Moore, F. D., *New England Journal of Medicine*, 1963, **269**, 1.
- 92 Dao, T. L., Tan, E., and Brooks, V., *Cancer (Philadelphia)*, 1961, **14**, 1259.
- 93 Forrest, A. P. M., et al., in *Prognostic Factors in Breast Cancer*, ed. A. P. M. Forrest and P. B. Kunkler, p. 186. Edinburgh, Livingstone, 1968.
- 94 Atkins, H. J. B., Falconer, M. A., Hayward, J. L., MacLean, K. S., and Schurr, P. H., *Lancet*, 1966, **1**, 827.
- 95 Sellwood, R. A., et al., *British Journal of Surgery*, 1968, **55**, 870.
- 96 Atkins, H. J. B., et al., *Lancet*, 1960, **1**, 1148.
- 97 Atkins, H. J. B., in *Clinical Evaluation in Breast Cancer*, ed. J. L. Hayward and R. D. Bulbrook, p. 214. New York, Academic Press, 1966.
- 98 Forrest, A. P. M., and Stewart, H. J., in *Major Endocrine Surgery for the Treatment of Cancer of the Breast in Advanced Stages*, ed. M. Dargent and C. I. Romieu, p. 89. Lyon, Simep Edn., 1967.
- 99 Huggins, C., and Dao, T. L.-Y., *Annals of Surgery*, 1954, **140**, 497.
- 100 Bulbrook, R. D., Greenwood, F. C., Hadfield, G. J., and Scowen, E. F., *British Medical Journal*, 1958, **2**, 12.
- 101 Bulbrook, R. D., Greenwood, F. C., Hadfield, G. J., and Scowen, E. F., *British Medical Journal*, 1958, **2**, 15.
- 102 Brown, J. B., Falconer, C. W. A., and Strong, J. A., *Journal of Endocrinology*, 1959, **19**, 52.
- 103 Block, G. E., Vial, A. B., McCarthy, J. D., Porter, C. W., and Coller, F. A., *Surgery, Gynecology and Obstetrics*, 1959, **108**, 651.
- 104 Pearson, O. H., and Ray, B. S., *American Journal of Surgery*, 1960, **99**, 544.
- 105 Fairgrieve, J., *Surgery, Gynecology and Obstetrics*, 1965, **120**, 371.
- 106 Moore, F. D., Woodrow, S. I., Aliapoulos, M. A., and Wilson, R. E., in *Carcinoma of the Breast*, p. 45. London, Churchill, 1968.
- 107 Bulbrook, R. D., Greenwood, F. C., and Hayward, J. L., *Lancet*, 1960, **1**, 1154.
- 108 Miller, H., Durant, J. A., Jacobs, A. G., and Allison, J. F., *British Medical Journal*, 1967, **1**, 147.
- 109 Atkins, H. J. B., et al., *Lancet*, 1968, **2**, 1255.
- 110 Wilson, R. E., and Moore, F. D., in *Prognostic Factors in Breast Cancer*, ed. A. P. M. Forrest and P. B. Kunkler, p. 399. Edinburgh, Livingstone, 1968.
- 111 Dao, T. L., in *The Human Adrenal Gland and Its Relation to Breast Cancer*, ed. K. Griffiths and E. H. D. Cameron, p. 99. Cardiff, Alpha Omega, Alpha, 1969.

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