volume is to be reduced by 90%. Anything less than a 99% kill-rate would therefore be called a failure of clinical response, and the finding of œstrogen receptor in such cases would be called a false positive.

There are several tumour or host factors which can contribute to a submaximal clinical response. If the proportion of proliferating cells is low (as in a scirrhous tumour) the degree of tumour shrinkage will be less. This will happen also if there is poor vascularity of the tumour associated with areas of necrosis or if the cell cycle is prolonged (as it often is with hormone-sensitive tumours). Again the degree of regression is often found to be less at some sites of metastases than others, presumably because of different metabolic factors.

I do not think we will ever achieve 100% correlation between positive œstrogen-receptor assay and "acceptable" clinical response with current methods of treatment. The present average figure of 55% correlation is rightly regarded as disappointing, but in my opinion it is mainly a reflection of the clinical criteria of response which we have set ourselves. It is influenced only to a small extent by problems in the assay of œstrogen-receptor protein. I believe that when we have more accurate criteria of clinical response than decrease in size of a lesion (which is cytokinetically the resultant between tumour-cell proliferation and cell death), we will find a considerably higher degree of correlation. I look forward to that day.

Department of Radiotherapy and Oncology,
St. Thomas' Hospital, London SE1 BASIL A. STOLL

COMPUTERISED TOMOGRAPHY IN METASTATIC BREAST CANCER

SIR,—We read with interest the speculation by Dr Bunting (July 23, p. 193) on the role of computed tomography (C.T.) in the assessment of carcinoma of the breast.

In our comparative trial of C.T. and mammography in women presenting with lumps in the breast[1,2] none of the patients who were found to have carcinoma at operation had C.T. evidence of parasternal or internal mammary lymph-node enlargement, and in all the patients in whom C.T. predicted axillary lymph-node enlargement, lymph-nodes were detected by palpation.

C.T. at its present stage of technical development does not allow differentiation between normal lymph-nodes and lymph-nodes affected by metastases. It can only demonstrate lymph-node enlargement.[3,4]

Our experience of scanning patients who present with lumps in the breast and patients with abnormal radioisotope bone scans suggests that C.T. has a useful and complementary role with other imaging techniques in the assessment of patients with carcinoma of the breast. The use of computed tomography in demonstrating the extent of advanced disease is an important therapeutic advance.[3,5,6]

Department of Diagnostic Radiology,
University of Manchester,
Medical School,
Manchester M13 9PT J. J. K. BEST
IAN ISHERWOOD

Professorial Surgical Unit,
University Hospital of South Manchester,
Manchester M20 8LR R. A. SELLWOOD

1. Best, J. J. K., Asbury, D. L., George, W. D., Sellwood, R. A., Isherwood, I. *in* Proceedings of 1st European Seminar on Computerised Axial Tomography in Clinical Practice (edited by G. H. Du Boulay and I. F. Moseley); p. 416. Berlin, 1976.
2. Best, J. J. K., Isherwood, I., Hartley, G., Asbury, D. L., George, W. D., Sellwood, R. A. Unpublished.
3. Kreel, L. *Clin. Radiol.* 1976, 27, 421.
4. Schaner, E. G., Head, G. L., Doppman, J. L., Young, R. C. *J. comput. axial Tomogr.* 1977, 1, 176.
5. Chernak, E. S., Rodriguez-Antunez, A., Jelden, G. L., Dhaliwal, R. S., Lavik, P. S. *Radiology*, 1975, 117, 613.
6. Jelden, G. L., Chernak, E. S., Rodriguez-Antunez, A., Haaga, J. R., Lavik, P. S., Dhaliwal, R. S. *Am. J. Roentgen.* 1976, 127, 179.

PREDOMINANCE OF LEFT-SIDED BREAST TUMOURS

SIR,—The paper by Dr Ing and his colleagues[1] on unilateral breast feeding and breast cancer raises some interesting questions about the laterality of breast carcinoma. As they say, others have found a small but significant predominance of left-sided tumours:

Area	*L*	*R*	*L/R*	*P*
Females				
Europe (7 studies)[2]	8413	7484	1·124	<<0·001
North America (18 studies)[2]	6693	6465	1·035	<0·05
Colombia[2]	256	230	1·113	N.S.
Japan[2]	314	265	1·185	<0·05
Hongkong[1]	1169	1203	0·972	N.S.
Males				
North America[2,3]	177	125	1·416	<<0·01
Britain[2]	53	47	1·128	N.S.

For the American and European data on female breast cancer there is a significant excess of left-sided tumours, the difference between the groups also being significant (P<0·001). For male breast cancer there is a significant excess of left-sided tumours only in the American sample, although the difference between the groups does not reach significance. The Japanese study gives evidence for a left-sided excess in at least one Asian country. These differences between groups might well represent genetic differences, particularly since there is evidence that laterality of breast carcinoma is inherited,[4-6] although not all studies have found this.[7] A summary of the data of these studies also reveals a trend, not previously reported, towards a difference between the two breasts. Briefly, a relative is more likely to be affected in the same breast as the propositus only if the propositus has a left-sided tumour. This bears a formal similarity to some of the problematic data associated with the inheritance of handedness.[8]

Side of tumour in propositus	*Side of tumour in relative*		*Same/ opposite*	*P*
	Same	*Opposite*		
L	57	27	2·111	<0·005
R	55	38	1·447	N.S.
Total	112	65	1·723	<0·001
Left *vs.* right: N.S.				

The Tanka women nurse with the right breast only and they have a higher incidence of left-sided breast cancer. However they also represent an ethnically separate people and it is thus possible that their left-sided breast carcinomas are related to their gene pool rather than to their behavioural peculiarity. To separate these two hypotheses would require the rigour of a laboratory experiment and would require half of the population to breast feed with their left breast only.

Laterality of breast carcinoma seems to manifest most strongly in one histological subgroup. The combined results of two studies[7,9] give the following:

Histological type	*L*	*R*	*L/R*	*P*
Adenocarcinoma	80	45	1·778	<0·01
Epithelial carcinoma ("carcinoma solido")	284	303	0·937	N.S.
Adenocarcinoma *vs.* epithelial: P <0·01				

1. Ing, R., Ho, J. H. C., Petrakis, N. L. *Lancet*, 1977, ii, 124.
2. Garfinkel, L., Craig, L., Seidman, H. *J. nat. Canc. Inst.* 1959, 23, 617.
3. Langlands, A. O., and others *Clin. Radiol.* 1976, 27, 21.
4. Busk, T. *Ann. Eugen.* 1948, 14, 213.
5. Penrose, L. S., MacKenzie, H. J., Karn, M. N. *ibid.* p. 234.
6. King, M. C., Guirgis, H., Lynch, H. T., Petrakis, N. L. Unpublished.
7. Anderson, V. E., Goodman, H. O., Reed, S. C. Variables Related to Human Breast Cancer. Minnesota, 1958.
8. Annett, M. *Br. J. Psychol.* 1974, 65, 129.
9. Bucalossi, P., Veronesi, U., Pandolfi, A. *Tumori*, 1954, 40, 365.

The effect of this result upon the familial data given earlier is not clear, but it is unlikely to negate it entirely since adenocarcinoma is a rare category. It is conceivable that the Tanka women also have a tendency to adenocarcinoma, thereby partly explaining their excess of left breast tumours.

Whilst it may be "inconceivable that the side on which breast cancer develops should influence a patient's likelihood of seeking medical attention", there is some evidence for precisely this, although Weinstein et al.[10] give few data. Garfinkel et al.[2] reported the following data:

Stage of tumour	*L*	*R*	*L/R*	*P*
I or II	311	322	0·966	N.S.
III or IV	233	187	1·246	<0·01

Stages I and II *vs.* III *and* IV: P=0·06

Perhaps I might reiterate the twenty-year-old plea of Garfinkel et al.[2] that the laterality of disease should be included as a standard item in the International Classification of Disease (perhaps as an extra digit), and certainly should be included as a part of all epidemiological research.

Psychological Laboratory,
University of Cambridge,
Cambridge CB2 3EB

I. C. McMANUS

ABO-DISTRIBUTION AND GEOGRAPHICAL DIFFERENCES IN DEATH-RATES

SIR,—As Mitchell has pointed out,[11] those parts of the British Isles in which the population contains a relatively high percentage of people with blood-group O tend to have higher death-rates from a number of causes, including atherosclerotic and coronary heart-disease, and the correlation is strong enough to be considered statistically significant. Mitchell suggests that population frequency of blood-group O be included among the variables to which a possible causal influence on geographic variation in mortality may be ascribed, and offers some results from multiple correlation analysis intended to separate a possible blood-group effect from the influences represented by longitude and water hardness.

Fortunately, it is possible to set an upper limit to the possible effect of variation in blood-group frequency by a simple arithmetic argument, and without resort to heavy statistical methods. The extreme values of blood-group O frequency in the data of Mitchell's fig. 1 are 41% and 54%. If we make the (absurd) assumption that all deaths occur in the group-O segment of the population, persons of other ABO types being immortal or at least immune to each particular cause of death under consideration, it then follows that variation in mortality attributable to variation in blood-group frequency can extend over a range from (41 × constant) to (54 × constant)—but no further. The factor 54/41, or 1·32, is small compared with the geographical variation that actually occurs, and small also in relation to the nearly twofold range of variation in mortality from heart-disease which the regression of death-rate on blood-group frequency purports to explain.

Coming closer to reality we may next assume that the mortality ratio between group-O subjects and others, rather than being infinite, is 2/1 (and it is hardly likely that a true value larger than this could have escaped recognition). Then the extreme range of geographical variation in mortality attributable to variation in blood-group frequency runs from ([2×41]+59) to ([2×54]+56), a factor of only 1·09. An effect of this magnitude would be of negligible importance in relation to the Twelve Towns Study.[2] Mitchell characterised the hard and soft water towns of that study as "ethnically divergent" on the grounds that blood-group O subjects are 47·15% of donors in the six soft-water towns compared with 45·11% in the hard-water towns. With an assumed 2/1 ratio between the death risk for group O and others this could produce only a 1·4% excess mortality in the soft-water towns. The actual excess (at ages 45–64) is 42% for cardiovascular disease and approximately 18% for all other causes of death.[12]

Faculty of Medicine,
Department of Preventive Medicine
and Biostatistics,
University of Toronto,
Toronto, Canada M5S 1A8

DAVID HEWITT
TERENCE W. ANDERSON

MATERNAL SERUM-ALPHA-FETOPROTEIN AND NEURAL-TUBE DEFECTS

SIR,—The report of the U.K. Collaborative Study on alpha-fetoprotein (A.F.P.) in relation to neural-tube defects[1] is welcome. However, the detection-rates for anencephaly and spina bifida may be considerably higher than those demonstrable when maternal serum-A.F.P. is used as a screening test for women attending a hospital antenatal clinic. We have done a prospective survey of 1844 consecutive women attending the Royal Maternity Hospital, Belfast, some 28 of whom had pregnancies associated with twins, anencephaly, or spina bifida.[2] Maternal serum-A.F.P. was measured at the first hospital antenatal visit, and the sensitivity of A.F.P. as a screening test for neural-tube defects at 15–19 weeks' gestation was 50%, taking the 95th centile of the A.F.P. distributions of normal pregnancy outcomes as the cut-off point separating normal from abnormal pregnancy. Reasons for this low detection-rate compared with those reported in the U.K. Collaborative Study include not only the sensitivity and specificity of the screening test but also the gestation-time at which the test is done (i.e., when women attend for their first antenatal visit). Some 53% of women in our study presented at the 14th week or earlier and another 19% did not appear at hospital until 20 or more weeks' gestation. In practice major modification of hospital antenatal clinic routine would be required to ensure A.F.P. screening at 16 weeks' gestation, irrespective of the problems of expanding facilities for amniocentesis and ultrasound investigation.

Department of Community Medicine,
Queen's University,
Belfast BT12 6BJ

J. H. ELWOOD

SIR,—The U.K. Collaborative Study provides valuable new data on α-fetoprotein (A.F.P.) levels. Using data on known abnormal outcomes (mainly anencephaly and spina bifida, A.S.B.) and on non-A.S.B. outcomes, the participants propose a cut-off procedure for deciding whether or not a particular pregnant woman should, on the basis of her serum-A.F.P., be encouraged to have a diagnostic amniocentesis.

This approach may be satisfactory when other observations are relevant to the decision or when the number of dichotomising criteria is so large that we can afford to be prodigal with the detailed information concerning any one criterion. Such prodigality may be justified, for instance, in classifying bacteria by the techniques of numerical taxonomy.

The A.S.B. situation is different. The final probability of an A.S.B. birth does depend on other observations. For any pregnant woman, it depends on the population's A.S.B. prevalence at birth—in her part of the country, and at her age, and with her family history and social circumstances. Table x in their paper shows that the study participants are to some extent aware of this. But why make two decisions—i.e., choose a cut-off point, then return to simple odds for the real decision—when one will do?

10. Weinstein, S., Vetter, R. J., Sersen, E. A. *Neuropsychologia*, 1970, 8, 185.
11. Mitchell, J. R. A. *Lancet*, 1977, i, 295.
12. Stitt, F. W., Clayton, D. G., Crawford, M. D., Morris, J. N. *ibid.* 1973, i, 122.

1. U.K. Collaborative Study. *Lancet*, 1977, i, 1323.
2. Bond, E. B., Thompson, W., Elwood, J. H., Cran, G. W. *Br. J. Obstet. Gynæc.* (in the press).