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# *Letter to the Editor*

The Letter to the Editor by Peter B. Dent and Peter B. McCulloch was shown to Dr. J. Maxwell Anderson who offers the following reply:

# The Importance of Statistical Evaluation and Experimental Design in the Interpretation of Data from Cancer Microdetector Studies

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WE FEEL that a most helpful aspect of our studies of putative microdetectors of cancers is in stressing the importance of methods and of experimental design. How data are collected and assessed critically affects the conclusions of such studies and both factors must be strictly controlled.

The interpretation of our PAM and CEA time-trajectories and of the data, made by Drs Dent and McCulloch is only one of a number of ways of assessing them. It is possible to illustrate an even greater advantage for PAM than we describe by using a cut-off level of say 55% increase in PAM, so that *all* metastatic patients would be classified correctly and only six of the clinically well would be misclassified (see Table 1, *Europ. J. Cancer* **15,** 712, 1979). It is also possible to attempt to select so-called normal ranges for PAM and CEA and consider only those measurements which are "abnormal", thereby failing to utilise all the information contained in the collected data. We have preferred to take a middle course, neither favouring one of the two tests nor neglecting to use the data fully.

The alert times for $\geqslant 75\%$ rises in PAM before clinical detection of metastases were less than 1 month in two of our metastatic patients and 1.5–11 months in eight. Dent and McCulloch's point about "... five of eleven patients who have a sustained increase ..." highlights only part of the findings. Dent and McCulloch also indicate that there is no difference between the specificities of PAM and CEA because two or more elevations of both occurred in similar proportions of clinically well patients—again this is a negative and limited aspect of a larger picture. The objective is to distinguish metastatic from well patients at an early stage and the method of analysis must be chosen accordingly. Our assessment of maximum rises offers such a positive method of possible clinical value. The use of percentage increases from a baseline, that in our experience is not influenced by mastectomy (*Brit. J. Surg.* **63,** 819, 1976), means that each patient acts as her own control. This is preferable for PAM since the range seen in our mammary cancer-bearing population is so large compared to the ranges seen in individuals.

Our study has expanded greatly and we have published an assessment of sixty stages I or II mammary cancer bearers followed for up to 10 yr after mastectomy [Anderson and Gettinby, *Carcino-Embryonic Proteins*, (Edited by F. G. Lehman) Vol. II, P. 625, 1979]. The results for PAM are illustrated in the figures reproduced by permission of

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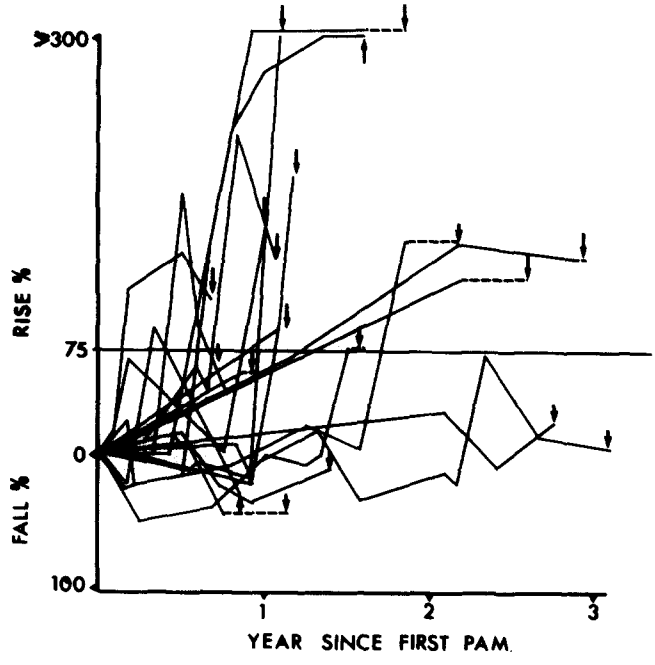


*Fig. 1. PAM profiles in the metastatic group. Arrows indicate time metastages became clinically obvious.*

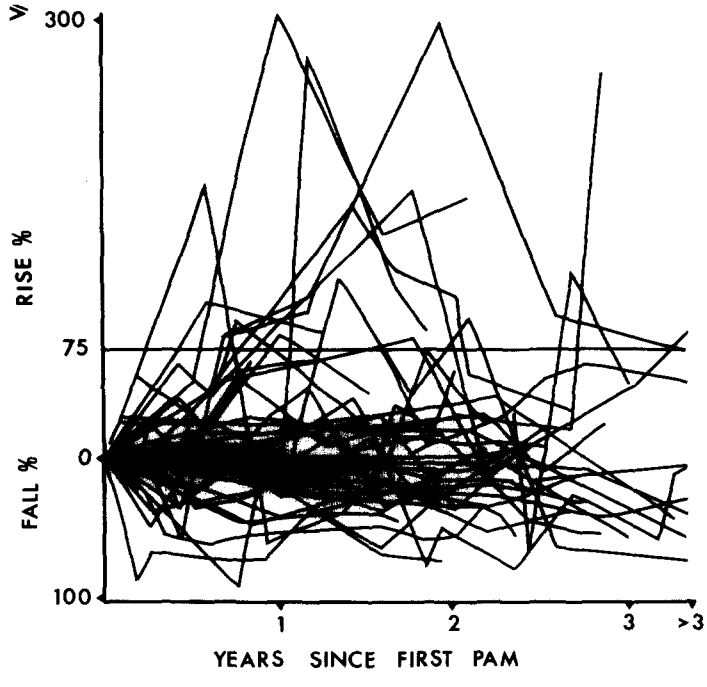


*Fig. 2. PAM profiles in the well group.*

Elsevier/North Holland, Biomedical Press. A Mann-Whitney U-test upon the maximum percentage changes from baselines in the metastatic group before the development of metastases against those in the clinically well group at any time, gave a value of $P<0.01$. Discriminant functions were applied to precisely comparable data for CEA without finding important differences. Our current assessment of PAM is that a 75% rise above initial individual blood levels carries an approximately 2 to 1 chance of the appearance of macrometastases during the subsequent 1.5–15 months.

It is of the greatest importance in studying putative microdetectors to fulfil three cardinal principles (Anderson, *J. roy. Soc. Med.* **72,** 314, 1979): (1) the establishment of valid baseline levels—generally the means of three or four separate initial evaluations; (2) the use of index numeration to test subsequent changes; and (3) the comparison of clinically well patients with those developing macrometastases. The reassessment of parts of our study by Dent and McCulloch fails to recognise these important features. It raises relatively unimportant aspects of a broadly based study which has already been doubled in size and follow-up with confirmation of the earlier findings.

*This reply closes the controversy.* The Editor.