[23–25] found an association between microvessel density and survival. Goulding and associates [24] also evaluated random field selection and image analysis to provide an objective and unbiased estimate, but found no relationship with survival.

The other problem relates to the heterogeneity of breast cancer and the need to take into consideration stage, age and type of carcinoma. This is well illustrated by the carefully documented study of infiltrating lobular carcinomas [25] which failed to show any associations between microvessel density and prognosis in this specific group.

The evidence to date about the value of microvessel counting is still inconclusive. The main problems appear to relate to evaluation. Until these are overcome the assessment of microvessel density is not an appropriate test to use outside of a very limited number of laboratories. Also, a static count of microvessel density does not necessarily reflect the dynamic process of metastasis. Seeking information about the factors stimulating angiogenesis, which may be targets for therapy, would appear to be a more profitable approach.

In conclusion, determining microvessel density in human tumours is not clinically useful.

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PII: S0959-8049(97)10042-9

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ELLIS IN his elegant article (pp. 609–613) highlights the theoretical issues which are the basis of the potential relevance of the determination of angiogenic activity in human neoplasia. Bi-directional research from the laboratory to the clinic provides rapid information on the pivotal role of angiogenesis in tumour growth, progression and metastasis, as well as on anti-angiogenic therapy [1].

Received 6 Aug. 1997; accepted 12 Aug. 1997.

Angiogenesis involves multiple sequential mechanisms stimulating the growth of host endothelium [2]. Therefore, the complexity of the phenomenon makes it difficult to develop a single functional assay which covers all the steps involved [3], as well as the identification of a single surrogate marker capable of predicting the efficacy of angioinhibitory agents [4]. This has to be taken into account in order to understand the potential advantages and limits of presently available methods to assess angiogenic activity.

Recent studies of translational research has allowed the validation in the clinic of some results observed in experimental models: (i) the determination of intratumoral microvessel density (IMD) or of angiogenic factors has proved that neovascularisation and hormone pathways independently stimulate breast cancer growth [5–7]; (ii) p53 regulates angiogenesis in some tumour types [8]; and (iii) laminin [9] and integrins [10] are components of the extracellular matrix involved in tumour cell invasiveness, metastasis and angiogenesis.

The angiogenic 'switch' may occur at different times during tumour growth. In certain models, it is involved in the transformation of normal cells into neoplastic ones [11], whilst in others, it is necessary in later stages, favouring tumour invasiveness and progression [12]. A measure of angiogenic activity detectable in body fluids is, therefore, a potential useful tumour marker for early diagnosis of cancer, as suggested by early clinical studies [13]. Most of the retrospective studies have shown that assessment of IMD in a tumour provides prognostic information [14]. The degree of IMD has been extensively studied in breast cancer with discordant results. However, the majority of the published studies found a statistically significant association of highly neovascularised tumours with poor prognosis [14, 15]. Until now, IMD has been determined in approximately 5000 patients with operable breast cancer and 72% of the studies found that it was a statistically significant prognostic indicator [15].

The nine studies reporting negative results on the prognostic value of microvessel count included six series of both axillary node-negative and node-positive patients (multivariate analysis was carried out in only two studies) [16–21] and three series of node-negative patients (multivariate analysis was carried out in only one study) [22–24]. Only one of these studies evaluated more than 200 cases [19]. In the interpretation of the results, this knowledge is important, as a valid evaluation of a new prognostic marker requires an adequate number of cases and a sufficiently long period of follow-up [25]. Indeed, the main end-point of a prognostic study is to verify whether the determination of a new prognosticator adds significant information over conventional markers. Therefore, the studies without a multivariate analysis do not permit any definitive conclusion to be drawn on the clinical significance of the marker under evaluation nor do they allow validation of the usefulness of standard markers in the cohort of patients studied.

Walker in the contra-article (pp. 614–615) mentions some points against the clinical usefulness of the determination of angiogenic activity in human tumours, by focusing the criticisms on the assessment of IMD in breast cancer. The position assumed by Walker in the contra-article is coherent with another editorial published in 1996 [26] and is in agreement with the criticisms also raised by Page and Jensen [27] on the methodology.

Both Dr Ellis and Professor Walker state that data from retrospective studies are difficult to evaluate, because of the different methods of detection of IMD and the heterogeneity of the characteristics of the patients. I agree with this view, as meta-analyses on retrospective studies are subject to several biases also related to the different treatments administered, lengths of follow-up and the criteria used to define a tumour as highly or low vascularised. However, the reader needs to be advised that the above considerations are to be extended to the evaluation of any new prognostic indicator and that, at present, very few markers have been evaluated prospectively [25].

Microvessel count has been evaluated in several solid tumours other than breast cancer. Even if the number of cases studied in each single tumour type is much lower when compared with that of breast cancer, again, the number of positive studies largely outnumbers those that are negative in lung, gastrointestinal and genitourinary cancers [28–30].

The capability of stratifying patients with the identification of subgroups who are more likely to benefit from adjuvant treatments is another promising clinical application of microvessel count. Preliminary retrospective studies suggest that patients with highly vascularised breast cancer have poor prognosis even if treated with conventional adjuvant therapy, independently of nodal status and levels of hormone receptors [31–33].

An optimal *in vivo* assay to monitor the activity of anticancer therapy needs to be repeated several times for long-term quantification of angiogenic activity prior to, during and after therapy. Because quantification of IMD is a static measure performed on tissue sections, it may be a suboptimal method for such a purpose. Moreover, even though it remains to be proven whether inhibition of angiogenesis is really an effective new anticancer therapy of human tumours, it has been suggested that the assessment of a surrogate marker of angiogenic activity is an integral part of the study design of the development of new anti-angiogenic drugs. This strategy could help to rationalise the clinical indications and to optimise the duration of administration of such compounds [34].

The most controversial issue concerns the prognostic value of microvessel count. The biological pre-requisites and the importance of study design for proper selection and clinical validation of a new biological prognostic indicator have been previously reviewed [25]. The most important steps are summarised in Table 1. A key question is if there is proof that determination of IMD is related to functional markers of angiogenesis. An adequate answer requires the combined assessment of IMD, angiogenic factors and endogenous angiogenesis inhibitors. No clinicopathological study has completely met the above study design yet. However, several studies documented that highly vascularised tumours are significantly associated with the expression of angiogenic peptides [35–37], elevated levels of plasminogen pathway [38] and with tumour cell shedding into effluent venous blood during surgery [39], or inversely related to the expression of endogenous angiogenesis inhibitors, such as thrombospondin-1 [40].

Is the present method of determination of IMD optimal and standardised? If not, what are the suggested steps to improve methodology? Moreover, is it feasible to propose a method of choice for future prospective studies? A comprehensive overview dealing with the above questions has been

Table 1. *Selection and validation of new prognostic indicators*

General criteria	
Issue	Steps met by microvessel count
Is the new marker related to a key mechanism involved in tumour growth, progression or metastasis?	Yes
Is the assay a validated measure of the biological phenomenon to be investigated?	Yes
Is the assay detectable by a specific, sensitive, reproducible method with quality controls applied?	Partially
Does the new marker add prognostic information over conventional prognostic indicators?	Yes
Are the results of the assay easily interpretable and useful to stratify subgroups of patients with the same tumour type and stage of disease but characterised by different prognoses?	Yes
Any prospective evaluation?	No
Criteria to evaluate the quality of each single study on microvessel count in patients with breast cancer	
Issue	Examples of studies with methodological pitfalls
Was the assay performed correctly?	[16, 18, 22, 24]
Was the cohort of patients studied sufficiently large in size?	[16, 21–24]
Were the characteristics of the patients sufficiently homogeneous?	[16, 18, 21]
Was the series unselected and made up of consecutive cases?	[16, 19, 21, 23]
Was the impact of treatments considered?	[16, 18, 19]
Were the results evaluated by a proper statistical analysis?	[16, 18]
Was a multivariate analysis performed on an adequate number of cases?	[16–18, 21, 23, 24]

recently published and an international consensus among experts has been reached on the standard method to be used for future prospective collaborative studies [3]. It was agreed that once the 'hot spot' is identified, it is possible to facilitate the evaluation of IMD using computer image analysis systems [41] or by a microscope eyepiece with a 25 Chalkely points graticule [42]. One study provided evidence that the Chalkley score may be applied in series from different centres with a good degree of agreement among pathologists and with prognostic value [32]. The above mentioned technical procedures should allow the biases related to the subjectivity of evaluation to be minimised. However, other promising methods of detection of angiogenic activity have been developed and are under evaluation. Some examples include the assessment of angiogenic peptides in the cytosol of primary tumours using quantitative immunometric assays [43]; the expression of specific integrins involved in angiogenesis [44]; the evaluation of novel antibodies recognising activated/proliferating endothelium [3]; and the use of contrast-enhanced magnetic resonance imaging, capable of detecting microvascular permeability within a tumour mass [45].

In conclusion, at present, no marker of angiogenesis has yet to be included in the panel of prognostic indicators used for the selection of patients at high risk or for current therapeutic decision, outside of proper clinical studies. However, IMD is one of the more promising prognostic markers and it merits evaluation in prospective clinical trials in patients with solid tumours. Future studies should also compare prospectively, in the same series, the prognostic value of IMD with that of other promising methods based on immunometric assays [43] or other quantitative techniques [45].

The *current* clinical applications of angiogenesis research are in their infancy, but assessment of angiogenic activity is of *potential* importance in the care of the cancer patient. How much angiogenesis will influence clinical decisions in oncology will be related to advances in understanding the biological mechanisms involved in angiogenesis; the development of standardised methodologies of detection with quality control, proof of the effectiveness of angiosuppressive therapy, and the capability of performing well-designed studies of translational research in the years to come.

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Acknowledgements—The research on angiogenesis was supported in part by grants from the Associazione Italiana per la Ricerca sul Cancro (AIRC), Milan. The author wishes to thank Mrs Daniela Mazzocco and Miss Lucia Regolin for the preparation of the paper.