What's happening in breast disease research? A bewildering array of efforts are taking place in many disciplines with an erratic unity of purpose. Indeed, the seeming diversity of research efforts is nearly incomprehensible to all but a few. These few would be among those who track the several hundred studies that are published each month concerning breast diseases, predominantly of the neoplastic type. The papers that seek to review and integrate these diverse data are few, and when superb efforts, such as the recent one by Harris and co-workers are published, they contain bits and pieces that would not achieve consensus in a small room of diverse parties.

We may need to seek some historical perspective to understand why this situation may be qualitatively and quantitatively different from other fields that have achieved better integration. Within the memory of most living practitioners of medicine, breast disease was unchallenging—a well-coordinated quilt. Twenty years ago there was one major controversy, and that was whether a modified radical mastectomy was equal to a full or complete radical mastectomy, which had been described in the 1890s. Only pathologists and surgeons were concerned with breast disease, in addition to radiation therapists with some mild and geographically varied interest. Most people accepted three diseases of the breast: cancer, yes; cancer, no (usually involving cysts); and fibroadenoma. There were two procedures to apply to this situation: breast biopsy and mastectomy. As has been stated by others, the paradigm developed by Halsted held sway and retarded interest in developing and understanding breast disease further. In the past few years we have moved from the 75 years in which the Halstedian paradigm was prevalent, through a paradigm that stated all breast cancer was metastatic from its inception, to a realization of the heterogeneity of diseases we call breast cancer. We can hardly fault Halsted for the length of time that his ideas held sway. Rather, it was our fault through those generations that we were lulled into complacency in believing that a question had been answered. The most important current insight is that there are many questions, and not merely one.

Some perspective in the evolution of understanding as reflected in the history of medicine and the history of science may provide insight for the interpretation and understanding of the current fast-moving, uncoordinated patchwork quilt of breast cancer research. Specifically, it is well-known to students of the history of science that its evolution is rate-limited by technology and insight. Thus, a good idea may await a specific technology to allow it to develop or to be tested. The testing in the biologic and medical sciences is particularly prolonged and demanding. Presently, although it seems to be a cliche, part of the testing process involves cost considerations. Thus, we now have techniques in abundance and exciting theories aplenty, but often, the rate-limiting step is the availability of patient resources and funding to adequately test practical utility.

For example, prognostic indicators have direct relevance to this discussion. Their added usefulness despite the great promise of the initial papers, may not significantly facilitate clinical decision-making after adequate testing has been done. Although it will not be the major purpose of this essay to discuss prognostic indicators in depth, let us just say that we have rapidly passed through a time when virtually any new indicator that was proposed was met with enthusiasm. After 2 or 3 years of being offered these new possibilities, the public is more discerning—it is a professional public with a better understanding of the usefulness of the major prognostic indicators that are already available, such as size, nodal status, histologic pattern, hormone receptors, and flow data.

So where in this patchwork quilt do the three papers on breast disease in this issue of the American Journal of Clinical Pathology belong? An analysis of their methodology, study design, and the questions they pose may allow them to be assigned to different time periods in the history of breast cancer research. The paper by Siitonen and associates documenting regional variations in cell proliferation within breast carcinomas provides a useful combination of high-technology and the insight that the process of cell division and multiplication occur preferentially at certain places within a tumor mass. The use of automated image analysis gives extra credibility to the future usefulness of this technique and provides more certainty to the end result or conclusion. This observation, however, is by no means new, and it is a foundation stone of the methodology used by Elston and colleagues for several years to grade breast carcinomas for useful
prognostication. Heterogeneity also is demonstrated by many other techniques.

The paper by Raff and co-workers may be part of the completion of a chapter begun in the 1980s on serum markers, particularly those related to transferrin. These authors demonstrate that the transferrin-receptor level is not altered with breast cancer. It is appropriate that a cautionary paper be published in the area of practical testing for breast cancer. A large body of literature involves the hope that something in the blood will be helpful in the diagnosis and prediction of disease progression in breast cancer. Most have not achieved routine clinical use. This clearly written paper focuses on a single question and has a direct rationale. It may not be exciting to demonstrate that a good idea is not useful in practical application, but to paraphrase a famous quote, science is the murder of promising ideas by ugly facts.

Finally, having cited papers that related best to the philosophy of the 1990s and the 1980s, we have come to the paper by Anastassiades and colleagues on the multicentricity of breast cancer. This paper is passé, irrelevant, and could have been written in the 1950s. No mention is made of the important fact that many, many papers involve conservation treatment of breast cancer. These studies, in which the majority of the breast is left behind after local extirpation of the cancer, have achieved general agreement and acceptance around the world. Breast conservation leads to a slightly varied recurrence rate within the breast, but one that involves a 95% predominance of recurrence in the area of the original tumor. This is assumed to be a reflection of the original neoplasm and not a separate primary tumor. Indeed, the prognoses of mastectomy and cell lumpectomy with radiation are taken to be virtually identical, so that considerations of psychological impact are appropriate. The paper by Anastassiades and associates relies on concurrent evidence in a study design that is severely flawed. The authors incorrectly refer to their study as prospectively designed, but patients are not followed for the development of anything. We are not even told how the quadrants were separated and studied, or whether the problem of central lesions related to the nipple was taken into account. In other words, a four-quadrant tumor in the region of the nipple would, in the simplest study design, be present in four quadrants. The conclusion that conservation treatment is not indicated because of the multicentricity of breast cancer found in this study is much less acceptable today than it might have been 20 years ago, when the Halstedian myth reigned. Indeed, if cancers are multicentric at one point in time, why do they not evolve separately at different points in time?

A review of the three papers provides an excellent example of the diversity of the current literature on breast disease. One paper is similar to many efforts of the 1950s and 1960s; one paper helps to end a promising but impractical idea (or at least adds evidence to that end); and finally, one paper uses the techniques of the 1990s to demonstrate the regional differences in breast cancer. The heterogeneity within individual carcinomas is firmly embedded in the lore of breast cancer among pathologists, but perhaps is little-known to many practitioners with a recently developed interest in breast disease.

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REFERENCES