In our report a severely atypical lesion, bordering on ductal carcinoma in situ (*1*, figures 4 and 5), demonstrated lobular microarchitecture when viewed in its three-dimensional entirety (figure 3). This lesion was selected to illustrate that lesions precancerous to ductal carcinoma arise in the lobule and not in bigger ducts, as commonly believed. No doubt many pathologists would diagnose the illustrated lesion as ductal carcinoma in situ; however, when myoepithelial cells persist, we call the lesion severely atypical.

Only 154 of the 2612 atypical lesions reported (*1*, figure 1) showed the severe atypia depicted in the illustrations. About 95 percent of the statistical data we presented refer to lesions displaying mild and moderate atypia; these lesions have been described and classified, and they were given the names, atypical lobules, type A, grade 1, 2, and 3 (*2*). Therefore, our report cannot be construed as being confined to lesions that are carcinoma in situ as suggested by Rosier (*3*).

We do not intend to challenge facts allowing pathologists to differentiate between lobular and ductal carcinoma by their microscopic characteristics. These two entities of breast disease obtained their names from the way they look in the light microscope in the fully evolved in situ stages in which lobular carcinoma looks "lobular" and ductal carcinoma looks "ductal." However, ductal carcinoma looks ductal because the lobule in which it arose unfolded and became a sphere as the cancer grew. Such a sphere when cut and studied under the light microscope looks like a bigger duct.

The site of origin of ductal carcinoma is important since its precancerous stages undoubtedly would have a similar location. Identification and isolation of potentially precancerous lesions to ductal carcinoma make it possible to study their biological behavior as transplants in animal hosts (*4*). Elucidation of factors that can induce regression of precancerous lesions would appear extremely important especially if they had clinical application. Thus detection of precancer in the living woman and nonsurgical reversion of the disease at a precancerous stage associated with little morbidity would be an ultimate goal.

In summary, our purpose is not to challenge currently useful terminology or concepts of the surgical pathologist, but to broaden our knowledge of the precancerous stage of ductal carcinoma of the human breast.

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Erythrocyte Sedimentation Rates and Malignancy: Role of Age and Erythrocyte Aggregation

Riley's suggestion (*1*) that "ESR [erythrocyte sedimentation rate] enhancement occurs in association with malignancy but not in analogous benign conditions" fails to recognize the effect of age variations on the observed data. Gilbertsen (*2*) reported increasing ESR with age in a group of more than 4000 patients at the University of Minnesota Cancer Detection Center. Ninety percent of ESR values in females 45 to 49 years old were under 39 mm/hour, while the 90 percent range extended to 53 mm/hour in women 70 to 79 years old.

The incidence of breast cancer rises dramatically with age, as observed in the Third National Cancer Survey (*3*). Figures for the Minneapolis–St. Paul metropolitan area (*3*) show average annualized rates per 100,000 females of all races of 75.2 in women 35 to 44 years old, 233 in those 55 to 64 years old, and 380 in those 75 to 84 years old.

Data from my laboratory (*4*) on 660 consecutive breast biopsies showed malignancy rates of 6 percent in women less than 40 years old, 22 percent in women between 40 and 59 years old, and 45 percent in those more than 60 years old. The reciprocal figures represent percentage of benign lesions decreasing with age.

The bimodal distribution of ESR observed by Riley in the breast cancer patients may, as he suggested, correlate with age (before or after menopause). Such bimodal distributions of breast cancer with age have been observed in the Netherlands (*5*).

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Riley (*1*) concludes that clues for rational approaches to cancer therapy and diagnosis might be identified if the relationship of enhanced erythrocyte sedimentation rate (ESR) to neoplasia can be clarified. We believe that literature dealing with erythrocyte and particle aggregation may contribute to the clarification in that it points out that rapid settling rates reflect a close-packed system of cells or particles (*2*, *3*).

Riley's observation that neither viscosity nor rouleaux effects will account for increased ESR among patients with malignant disease is confirmed by our research. Further, our study of 565 samples of blood drawn from male patients undergoing routine physical examination disclosed an essentially trimodal as opposed to bimodal distribution of ESR's. This study raised the question of the desirability of measuring ESR's both on the basis of 24-hour and 1 hour observations (*2*).

In suspension systems, sedimentation of suspended particles, be they red cells, platelets, or nonbiological particles, can be accounted for by the state of their dispersion or aggregation present at the time the sedimentation rate is measured (*2*). On the matter of dispersion and aggregation, the International Union of Pure and Applied Chemistry (*4*) recognizes the following states: (i) dispersed, in which each cell or particle settles as an independent unit; (ii) coagulated, an aggregated state in which the cells or particles are in surface contact with each other and settle as compact units; and (iii) flocculated, in which cells settle as part of a network-aggregated system consisting of particles linked by bridging molecules.

Our observations of the settling properties of suspensions in these states indicate that coagulated aggregates sediment most rapidly, flocculated systems

at the slowest rate, and dispersed systems at a rate intermediate between the two (*5*).

Microscopic examination of rapidly settling whole blood of patients with malignancy discloses close-packed clumps of coagulated erythrocyte aggregates. These appear not as rouleaux but as clusters similar in appearance to grapes (*6*). The elevated sedimentation rate is due to these coagulated red cell aggregates, not to classic rouleaux formation which would ordinarily account for the rapid sedimentation rates observed in nondisease states.

If glycoproteins are added to normal in vitro samples of whole blood, formation of coagulated aggregates and rapid ESR's occur. In persons with neoplastic disease, the presence of large quantities of glycoproteins and other macromolecules on the surfaces of erythrocytes and other various cells produces the same effects and may account for Riley's observation.

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Foley's proposed explanation for erythrocyte sedimentation rate (ESR) elevation in cancer subjects represents an attractive simplification that does not appear to be supported by direct experimentation. The validity of his thesis relies upon a close correlation between a progressive elevation of ESR with increasing age and a corresponding increase in the incidence of breast cancer.

There is no question concerning the general increase in cancer incidence as a function of age, although in a discussion of aging and cancer, tumors of childhood and cancers of the breast, prostate, and testes were identified as exceptions (*1*). However, irrespective of the validity of such exceptions, ESR does not increase with age in healthy individuals to the same extent as does cancer incidence in the general population. Our early studies indicated, in the case of healthy adults, no substantial effect of age on ESR values (*2*).

These observations were confirmed by the studies of Peyman (*3*). He found that in normal healthy subjects of various ages, the ESR (determined by the Westergren method) for subjects 18 to 49 years old was 5.9 ± 0.2 (mean $\pm$ S.E.M.), whereas that for subjects 50 to 84 years old was 6.1 ± 0.3; there was no significant difference for males or females in respect to the ESR levels of the two age groups ($P > .05$).

The seemingly contrary observations of Gilbertson (*4*), cited by Foley, of higher ESR (Westergren) values and an apparently increasing ESR with age are not persuasive unless the state of health of the subjects is known, inasmuch as ESR is elevated in a wide variety of diseases and inflammatory conditions of the elderly (*5*). It is hazardous to rely on ESR ranges, since a small number of elevated values could prejudice the upper range of a large group of patients. To avoid the distorting influence of a few abnormal individuals, it is more appropriate to examine median values or frequency distributions. Median ESR values of six age groups reported by Gilbertsen were not dramatically different. For example, subjects 45 to 49 years old had a median ESR of 20, as compared with 29 for those 70 to 79 years old. Vignon's and van Zonneveld's studies indicate that such differences and any high values could be attributed to occult urinary tract infections or other medical problems (*5*). It is thus unlikely that the significant increase of ESR observed in a substantial segment of 385 patients with breast carcinoma (*6*) can be explained merely as a function of their age.

Ecanow and Gold report that experimental addition of glycoproteins to normal blood caused an increase in ESR analogous to the elevation noted in some breast cancer patients (*6*). This observation is consistent with my suggestion that the known association of glycoproteins with mammary carcinoma could account for the ESR abnormalities seen in such patients (*6*). However, patients with other varieties of cancer, such as lung and cervical carcinoma, also exhibit striking ESR elevations (*7*). This raises two important questions: Are similar glycoproteins associated with such neoplastic lesions, or are other unknown substances responsible?

The reported trimodal distribution of ESR values in Ecanow and Gold's normal male population is puzzling since our studies of more than 1200 male blood bank donors yielded only a single well-defined peak, skewed to the left (*2*, *7*). However, a conspicuously bimodal ESR distribution was observed in a small population of male lung cancer patients, with both peaks falling to the right of the normal mode (*2*, *8*).

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