criteria for the diagnosis of carcinoma *in situ*. While the finding of K-*ras* mutations in atypical hyperplasia would still be of great interest, it would not confirm the assertion of Yanagisawa et al[4] that such mutations occur in lesions not recognized morphologically as preneoplastic.

Furukawa et al[12] have proposed one possible solution to the difficulty of morphologically classifying proliferative ductal lesions. They have used morphometric analysis to evaluate architectural and cytological features and have stratified lesions into three groups representing increasing degrees of atypia. Unfortunately, morphometric analysis is a rather unwieldy technique, and probably will not be useful for routine evaluation of these lesions. Perhaps one alternative would be to recognize that a continuum of preneoplastic changes exists in the pancreatic ductal epithelium, as it does in the breast, cervix, prostate, and other epithelial sites. The use of "pancreatic intraepithelial neoplasia" or "PanIN" to refer to these changes might help avoid some of the variability of more descriptive terminology. Nonetheless, because of the data of Yanagisawa et al,[4] it is still unclear whether "hyperplasia without atypia" would represent the earliest preneoplastic ductal lesion (ie, "PanIN I") or, as the more descriptive term implies, a reactive proliferation. In fact, if experience with preneoplastic lesions in the pancreas parallels that with similar lesions in the breast,[13] it is unlikely that a consensus will ever be reached regarding histological criteria for atypical hyperplasia or carcinoma *in situ*. Unfortunately, the lack of uniform terminology for intraductal lesions will delay a consensus in defining the earliest preneoplastic proliferative lesion. For the immediate future we recommend that the classification being used be clearly defined or referenced, and that key or questionable lesions be illustrated.

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Author's Reply:

We appreciate the interest of Drs. Klimstra and Longnecker in our recent article describing the detection of K-*ras* mutations in mucinous pancreatic duct hyperplasia from a patient with a strong family history of pancreas cancer.[1] Klimstra and Longnecker correctly point out several of the factors that have hindered the identification of the precursor lesions to invasive pancreas cancer, including 1) a lack of consensus regarding morphological criteria for the diagnosis of specific proliferative duct lesions, 2) the confounding variable of infiltrating cancer admixed with intraductal lesions in many published series, and

3) the inability to study the natural history of histologically defined intraductal lesions. We believe that molecular analysis can potentially overcome these difficulties and may ultimately serve not only to define which proliferative lesions are neoplastic but also to permit assessment of whether these lesions represent precursors to invasive cancer.[1–3]

Because a neoplasm derives from a single clone of cells,[4] molecular analysis may be used to distinguish reactive pancreatic intraductal lesions from those that are truly neoplastic. Our finding of activating point mutations in K-*ras* in pancreatic duct lesions in the absence of invasive cancer,[1] therefore, suggests that these lesions are truly neoplastic. Similar findings have been reported by others,[5–8] effectively establishing that many of the intraductal lesions, which on morphological grounds alone would be classified as various grades of "mucinous duct hyperplasia," are indeed neoplastic. Along these lines, we applaud the suggestion of Drs. Klimstra and Longnecker that the term "pancreatic intraepithelial neoplasia" be adopted. This terminology correctly reflects the neoplastic nature of these lesions and should help to standardize terminology.

The identification of a neoplastic clone, however, does not necessarily imply malignancy. Therefore, it will be important to identify a means of predicting the likelihood that specific intraductal lesions will progress to invasive cancer. If we were able to predict the behavior of these lesions histologically, then a standard histopathological classification scheme would be clinically useful. Unfortunately, our understanding of the natural history of histologically defined duct lesions is hampered because, unlike the cervix, breast, and prostate, the pancreas is not readily accessible to biopsy. While we all may agree to classify a given lesion as PanIN 1, what should we tell the surgeon when such a lesion is identified at a margin?

We believe that the malignant potential of intraductal lesions can best be assessed at the molecular level, by prospective study of patients in whom screening tests reveal a genetic alteration, but whose clinical evaluation fails to identify a malignancy. Intraductal lesions have been shown to shed their DNA into the pancreatic juice and stool,[7,8] providing two methods of following the progression of the genetic alterations in pancreatic ducts. The molecular identification of potential precursor lesions to pancreas cancer may circumvent the difficulties inherent in assigning malignant potential to these lesions solely on the basis of histology. Our work thus far suggests that K-*ras* activation may be an early event in pancreatic intraepithelial neoplasia, while mutation of p53 may coincide with the development of carcinoma *in situ*.[1,3] This observation shows striking resemblance to the genetic model of the adenoma-carcinoma sequence in colonic neoplasms.[9]

In summary, molecular studies have demonstrated that many pancreatic intraductal lesions previously classified as various grades of "hyperplasia" are, in fact, neoplastic.[1] To reflect these recent findings, the nomenclature of these lesions should be changed from "hyperplasia" to "neoplasia." A challenge for future investigations will be to determine the propensity of specific intraductal neoplasms, as defined at the molecular level, for progression to infiltrating carcinoma. Given the mortality of infiltrating pancreas cancer, the potential benefits of meeting this challenge are enormous. Hopefully, through the use of molecular techniques,[10] early pancreatic neoplasms will one day be detected and treated *before* they become life-threatening.

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