

by the use of NIH/3T3 murine fibroblasts transfected with the complementary DNA coding for N-CAM, was not significant, and no difference was detected in the adhesion of  $\gamma\delta$ T cells to N-CAM<sup>+</sup> transfectants and wild-type NIH/3T3 cells (<10%). These findings would rule out the possibility of a homophilic adhesion mechanism operating in our system.

We also suggest a role for NCAM/CD56 in the "outside-in" signaling in  $\gamma\delta$  T cells. There is increasing evidence for a signal transduction through integrin-extracellular matrix (ECM) interaction. In this view, integrins, or other ECM receptors, might transmit signals by organizing the cytoskeleton, thus regulating cell shape and movement (7,8). We found that oligomerization of N-CAM/CD56 through the cross-linking obtained with the specific monoclonal antibody and an immobilized goat anti-mouse immunoglobulin, led to cell spreading and cytoskeleton rearrangement in most  $\gamma\delta$  lymphocytes. Pretreatment of N-CAM+/CD56 cells with either the F(ab')<sub>2</sub> fragment or the TA181H12 monoclonal antibody led to an inhibition of cell spreading and cytoskeleton rearrangement induced by immobilized anti-N-CAM antibodies (Table 1). These data would imply that N-CAM/CD56 can be considered an adhesive receptor responsible for outside-in signaling following lymphocyte-ECM interaction.

In conclusion, we hypothesize that N-CAM provides an additional mechanism for the extravasation of T cells. Heparan sulfate, among other ECM components, might contribute to the regulation of lymphocyte attachment to injured endothelium and extravasation into tissues where inflammatory or antitumor reactions take place (9). We would also propose that N-CAM functions as a membrane receptor whereby ECM proteoglycans can deliver signals leading to cytoskeleton rearrangement and modifications in the cell shape and motility, possibly affecting lymphocyte emigration.

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## Note

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## Re: Adenocarcinoma of the Esophagus: Role of Obesity and Diet

Brown et al. (1) describe obesity and dietary patterns as possible factors in the pathogenesis of esophageal adenocarcinomas. Adenocarcinomas of the esophagus are rare and must be clearly distinguished from carcinoma of the cardia or the esophagogastric junction. The study was originally designed to collect data on squamous cell carcinoma, and the presence of Barrett's

esophagus was not examined. Although Barrett's esophagus is probably the most important factor in both the etiology and the diagnosis of adenocarcinoma of the lower esophagus, it must be considered before classification. Brown et al. did not mention the criteria used by the pathologist for distinguishing the two localizations. Therefore, it remains unclear whether the 61 carcinomas are to be classified as esophageal tumors or as cancers of the cardia. The histologic type of the adenocarcinomas was not considered; however, as in gastric cancer, the pathogenesis and etiology of adenocarcinoma and signet ring cell carcinoma (both included in International Classification of Diseases for Oncology codes 8140-8573) (2) may be different (3,4).

Other factors, such as the patient's nutritional status or the two major histologic types, squamous cell carcinoma and adenocarcinoma, may be responsible for the significant differences in body mass index (BMI) values. Squamous cell carcinomas exhibit an advanced stage at diagnosis, and the patients may also be malnourished because of alcohol abuse. Improved surveillance of Barrett's esophagus may result in earlier detection of adenocarcinomas, rather than squamous carcinomas. Therefore, relationships between tumor stage and BMI values must be examined separately for both tumor types. Nevertheless, the pathogenetic mechanism described by Brown et al. (1) (obesity predisposing to hiatus hernia followed by Barrett's esophagus and carcinoma) appears relevant and emphasizes again the importance of detailed information about Barrett's esophagus. We think that large epidemiologic studies with subtle conclusions about possible etiologic factors cannot neglect the consideration of basic pathologic features.

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obesity and diet. *J Natl Cancer Inst* 87:104-109, 1995

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## Response

Drs. Dworak and Küspert are correct in indicating that our case-control study (1) of esophageal adenocarcinoma did not include an independent pathology review and that such a review would generally enhance the value of an epidemiologic study. We are confident, however, in the overall anatomic and histologic classifications of tumors from our study, which was conducted in areas participating in the Surveillance, Epidemiology, and End Results (SEER)<sup>1</sup> Program of the National Cancer Institute (NCI). This series of population-based cancer registries covers approximately 10% of the U.S. population and is the primary source of cancer incidence data used to assess demographic patterns of cancer risk in the United States. For this reason, all participants in the SEER Program meet formidable, specified criteria to ensure data accuracy and reliability, and they submit to a rigorous quality-control program,

including periodic reviews and audits of all aspects of data collection and analysis (2).

In our study, 113 cases were coded to the esophagogastric junction (International Classification of Diseases [ICD-O] site code 510), and 61 cases coded to the esophagus (54 cases coded to the lower esophagus, six to the middle, and one to multiple sites). Drs. Dworak and Küspert are concerned about the histology of the 61 cases of esophageal cancer, but they should be reassured that 53 (86.9%) were coded as adenocarcinoma not otherwise specified (ICD-O code 8140), and eight (13.1%) were coded as specific types of adenocarcinoma ICD-O codes 8200, 8260, 8480, 8481, and 8490), including only one signet ring adenocarcinoma (ICD-O code 8490).

Drs. Dworak and Küspert indicate that various reasons may exist for the difference in body mass index (BMI) values between subjects with squamous cell carcinoma and adenocarcinoma of the esophagus and that these reasons include alcohol abuse and stage at diagnosis, but such factors cannot explain the high BMI seen when the adenocarcinoma case subjects are compared with the population-based control subjects in our study. In addition, to address the possibility that changes in BMI may be associated with the diagnosis of cancer, we used usual rather than current adult weight to calculate BMI. If patients with adenocarcinoma were subject to recall bias and thus reported weights that were lower than usual because of concurrent disease, however, the true association with BMI would then be even stronger. Finally, we agree with Drs. Dworak and Küspert that more detailed information should be obtained about

precursor lesions, such as Barrett's esophagus, in future studies designed to identify the causes of esophageal adenocarcinoma.

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## Notes

<sup>1</sup>*Editor's note:* SEER is a set of geographically defined, population-based central tumor registries in the United States, operated by local nonprofit organizations under contract to the NCI. Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis.

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**Erratum:** "Mechanism of Synergy of Levamisole and Fluorouracil: Induction of Human Leukocyte Antigen Class I in a Colorectal Cancer Cell Line," by Abdalla et al. [*J Natl Cancer Inst* 87:489-496, 1995 (Issue 7)]. The last line of column 1 in Table 1 should read "5-FU, 0.4 µg/mL + levamisole, 1 µg/mL." The Journal regrets the error.



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