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Perspectives and Commentaries

Identification of Preneoplastic Changes

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(A COMMENT ON: Prat M, Griselli B, Rossino P *et al.* Expression of the monoclonal antibody-defined CAR-3 epitope on neoplastic and preneoplastic lesions of the colon mucosa. *Eur J Cancer Clin Oncol* 1987, **23**, 923–932.)

FOR a long time, it was hoped that, compared to normal cells, malignant cells would disclose differences that might help to identify them at an early stage or to kill them selectively. Although some differences at the biochemical level seem evident, the malignant cell does not appear in the present state of our methods to synthesize new molecular species or establish particular metabolic pathways [1, 2]. What makes the cells different seems so far to be of a quantitative rather than qualitative nature.

During the two last decades, considerable efforts have been made to identify these abnormalities. Most of the antigenic properties of the cell are due to the glycosphyngolipid (GSL) constituent of the cellular membrane. During malignant transformation, there is a modification of the GSL characterized by a shortening of the hydrocarbon chains due to a lack of a specific glycosyltransferase, which leads to the transformation of particular GSL absent or barely detectable in normal controls. Although the role of GSL in mediating the altered behavior of malignant cells is still speculative, many reports have attempted to correlate changes in cell surface GSL content or organization with the appearance of a transformed phenotype [3, 4].

Prat *et al.*, in a recent issue of this journal [5], have identified a monoclonal antibody, termed the AR-3 monoclonal antibody, which was previously found to be able to discriminate between neoplastic cells in gastric, pancreatic, colonic, ovarian and endometrial carcinomas and their normal counterparts [6]. The study included established colon cancers and adenomas with dysplasia of various grade. The results, in terms of accuracy, are, in our opinion, disappointing. Positivity of the test relies on the percentage of tissue stained and on the intensity of the staining. Thirty-eight per cent of the tumors are not stained or have less than 1% of the tissue stained, 71% had more than 50% positive tissue stained and/or a strong staining intensity, 33% had more than 50% positive tissue stained and at least a moderate staining intensity. One may see that, depending on the cut-off point that is chosen, the false negative rate may vary considerably.

In a former work, staining of normal tissues was observed and no explanation could be found [6]. In this series, normal tissue was not investigated [5]. The antigen recognized by the AR-3 monoclonal antibody in normal tissue or in benign adenomas would suggest that its expression might be related to cellular properties not specifically related to neoplastic transformation such as an increased proliferation rate, as is observed in adenomas and ulcerative colitis [7], or by unspecific inflammatory reactions. These aspects should be further documented.

Even if a high sensitivity was obtained, monoclonal antibodies, used as a probe for diagnosing malignant and potentially malignant tissue, might not be of great clinical interest: in malignant tissue, the diagnosis is established on the grounds of pathological characteristics and the detection of a tumoral antigen would be redundant. Using several different antigens as proposed by the authors

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makes the diagnostic procedure more complex without helping the clinician in making his decision.

In a premalignant situation, a lack of sensitivity makes an immunologic test useless. One knows, for example, that only a rather small fraction of the adenomas will actually undergo transformation after a period of about 15–20 years. Although it is still not known whether preventive resection of adenomas would have a significant influence on the incidence of colorectal cancer, the treatment, which is generally recommended considering the low risk of the procedure, is to resect them. The follow-up of adenomas on the basis of histology combined with monoclonal antibody testing would therefore appear unrealistic.

Ulcerative colitis is a disease where the multiplication of tests demonstrating malignant transformation at a stage that may be cured by surgery alone is of paramount importance. It has been shown that severe dysplastic lesions located on masses represent a major risk of cancerization and might lead to preventive colectomy [8]. However, dysplasia, as a marker of the definite malignant step, is not satisfactory. A large proportion of moderate dysplasia never progresses towards more severe stages and severe dysplasia may remain stable for a long period of time or even regress [9, 10]. New technical approaches allowing a clear-cut definition of malignant transformation are needed. An increase in the duration of the phase of DNA synthesis might offer an answer to this problem [7], but no prospective study has yet been undertaken to confirm this.

The only clinical situation where an immunological test may be of help, would be in those patients with a family history of colorectal cancer in whom the mucosa looks histologically normal. Identification of the antigen might justify more careful and regular screening.

The questions raised by a new immunological test, such as the AR-3 monoclonal antibody, reminds us unavoidably of the carcinoembryonic antigen (CEA). When Gold and Freedman [11] identified the CEA in 1965, there was great enthusiasm that this would herald a new era of earlier diagnosis of primary lesions and recurrent tumor. After more than 25 years, it has been established that CEA lacks specificity and, for example, a 30–60% incidence of elevated serum CEA was observed in patients with bronchitis, emphysema or alcohol addiction. There is no evidence to support the use of serum CEA levels in screening either in an unselected population or in high risk cases such as patients with adenoma or ulcerative colitis. If CEA may be helpful in surveying for recurrence, to date it has not been clearly shown to improve or replace a careful clinical follow-up of patients. One of the only fields of interest that remains to be investigated might be to label anti-CEA IgG and test its accuracy as a radioimmunodetector in patients with primary and metastatic colon cancer [12].

The successive steps leading to malignant transformation are not well known. At the present time, we can only identify some of the abnormal proteins (and probably only fragments of these) related to malignancy. Immunologic tissue and blood tests are not yet fully in use as diagnostic procedures. The lack of accuracy observed points out the difficulties in identifying anomalies specific to cancer. What is the significance of a negative test in a proven cancer? Does this mean that the marker which is tracked is not specifically linked to malignant transformation but to a corollary effect (loss of control to growing factors, changes in proliferative capability, etc.) which may vary from one cell line to another? Maybe more than one anomaly indicates a cancer process so that a given tumor might express predominantly one or another of these.

Research in this field must continue and clinical evaluation of new markers should be carefully investigated, not only in significant numbers of cancer samples and types but also in normal cells and in patients with benign diseases involving inflammatory processes and/or modifying the proliferation rate of the tissues, since all these factors may be responsible for a positivity of the test under study.

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