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DETERMINATION OF ANTI-MALIGNIN ANTIBODY AND MALIGNIN IN 1,026 CANCER PATIENTS AND CONTROLS: RELATION OF ANTIBODY TO SURVIVAL

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Subjects: Cancer patients and normal controls

Abstract

The antibody to Malignin, a cancer cell 10,000 Dalton polypeptide of known composition, was quantitatively determined

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blind by specific immunoadsorption in 1,094 serum specimens from 1,026 cancer patients and controls. Anti-malignin antibody, known to be cytotoxic to cancer cells *in vitro*, was elevated in 92.7% of sera from patients with clinically and pathologically active cancer (mean 273.7 ± 156.5 micrograms/ml) compared with healthy normal subjects (mean 59.1 ± 27.0 micrograms/ml). This supports the hypothesis that malignin is a general transformation antigen. The antibody was in the normal range (0 - 134 micrograms/ml) in 100% of sera of healthy normal subjects (first control group), in 94.6% of sera of hospital out-patient non-cancer controls (mean 64.3 ± 46.3 micrograms/ml) (second control group) and in 91.2% of sera of in-patient medical-surgical disorder non-cancer patients (mean 81.2 ± 67.3 micrograms/ml) (third control group). That only an active cancer state appears to be associated with elevated antibody levels is supported by the finding that the antibody was in the normal range in 94.2% of sera from cancer patients who had been successfully treated and clinically showed no evidence of disease at the time of the determination (fourth control group) (mean 70.1 ± 36.7 micrograms/ml). None of the four control groups was statistically significantly different from each other, but each control group differed from the active cancer group at a level of $p<0.000001$. The antigen, malignin, was correctly detected blind in 20 of 22 cell preparations by immunofluorescence with purified anti-malignin antibody. Of the 109 cancer patients who had antibody levels below 135 micrograms/ml, 90 (83.3%) were dead within one year (mean 4.4 ± 3.5 months). Of the 76 active cancer patients who could be followed and who were still alive beyond one year and up to 46 months (mean 22.0 ± 8 months) after the antibody determination, 68 (89.5%) had had antibody levels above 135 micrograms/ml. The relationship of the concentration of anti-malignin antibody to survival suggested by these data as well as some diagnostic and possible therapeutic implications are noted.

Introduction

A general transformation antigen is one which is common to the process of malignant transformation rather than to the particular cell type involved. The general antigen, therefore, differs from cell-specific tumor markers which are related to the products

of the particular type of cell transformed, as in the case of insulin or thyroid hormone excesses produced by pancreatic or thyroid neoplasms, respectively (Bogoch *et al.*, 1980). Malignin, a 10,000 Dalton polypeptide from malignant glial cells with a high content of glutamic acid and aspartic acid, and a high ratio of these two amino acids to histidine (Table I), was reported in 1975 (Bogoch, 1974, 1976, 1977). Its close structural relatives, Astrocytin, Recognin L (lymphoma) and Recognin M (mammary carcinoma) (Bogoch, 1977; Bogoch and Bogoch, 1979) are members of what appears to be the first chemically and immunologically defined family of general transformation antigens. These antigens, or Anti-malignin antibody which reacts with each, have been determined in the cells and sera of patients with a variety of neoplasms, in induced malignant transformations in animals, and in malignant cells and their supernates growing in tissue culture (Bogoch and Bogoch, 1979a, 1980; Bogoch *et al.*, 1979; Harris *et al.*, 1980). Other transformation antigens, not quite as general but broad in representation, are now being identified in other laboratories in experimental cell transformations induced by chemical and viral means (Langan, 1980; Rigby, 1979).

Over the past seven years, we have examined the possible relation of Malignin and Anti-malignin antibody to human cancer states. Tumor-associated antigens studied in man, such as the carcinoembryonic antigens (Krupey *et al.*, 1968) have exhibited varying demonstrability in different types of cancer. Perhaps due to the fact that none have had constant chemically defined composition or mode of production, the inconstantly released mixtures of antigens rather than a potentially more constant level of specific antibody had to be measured in serum. Malignin is produced in tissue culture of malignant cells, is of known composition, and its antibody can be isolated from the serum of patients with cancer (Bogoch and Bogoch, 1979, 1980). The antibody and antigen studies reported here support the apparently ubiquitous distribution of the malignin antigen or its very close structural relatives in active cancer of all types examined. In addition, because of the absence of previous direct evidence that a cancer antibody produced by the patient is beneficial to the patient, the possible relationship of quantity of Anti-malignin antibody to survival was examined.

TABLE I *

AMINO ACID COMPOSITION OF POLYPEPTIDES[a] PRODUCED FROM HUMAN MALIGNANT GLIAL TUMOR AND FROM THREE DIFFERENT TYPES OF MALIGNANT CELL GROWN IN TISSUE CULTURE: RESIDUES PER MOLECULE OF PROTEIN

	Astrocytin *(in vivo)* brain glioma)	Malignin *(in vitro)*[b] brain glioma)	Recognin M *(in vitro)*[b] mammary (MCF-7 carcinoma)	Recognin L *(in vitro)*[b] lymphocytic P_3J lymphoma)
Threo	5	5	5	5
Ser	6	5	5	5
½ Cys	2	1	1	1
Meth	1	2	1	1
Val	4	6	6	6
Ileu	2	4	4	4
Phe	3	3	3	3
Lys	8	6	6	6
His	2	2	2	2
Arg	4	5	5	5
Asp	9	9	9	8
Glu	13	13	11	10
Leu	8	8	8	7
Tyr	2	3	2	1
Pro	4	4	4	5
Gly	6	6	9	13
Ala	9	7	9	10
Total number Residues	88	89	90	92
Molecular weight calculated	9,690	10,067	9,870	9,606

[a] Specimens were hydrolyzed *in vacuo* with 6N HCl at 108°C for 12 hr. The nearest integer for the mole number of each amino acid is the average of two separate determinations. All above determinations were performed "blind" by the Boston University Medical Center central facility for amino acid analysis. Results obtained with 24-hr and 72-hr hydrolysis of malignin, at two additional laboratories, respectively, were not significantly different when serine, threonine, tyrosine, and cysteine were corrected for additional destruction by acid.

[b] Cells grown in tissue culture.

*From Bogoch and Bogoch, 1979

TABLE II

Distribution of Number of Serum Anti-Malignin Antibody Determinations According to Type of Malignancy and Clinical Status

TYPE OF MALIGNANCY	TOTAL NUMBER	CLINICAL STATUS		
		Active Disease	No Current Evidence Of Disease	Terminal
Carcinoma of:				
Lung	38	11	1	26
Larynx	3	2		1
Breast	67	26	27	14
Uterus	5	1	1	3
Cervix	6	3		3
Ovary	11	3	3	5
Vulva	1			1
Colon	37	18	3	16
Rectum	13	9	2	2
Stomach	2	1		1
Oesophagus	3	1		2
Bile Duct	1			1
Prostate	13	7	4	2
Bladder	12	5	4	3
Urethra	1	1		
Kidney	15	6	5	4
Testis	7	1	5	1
Thyroid	4	4		
Pancreas	4			4
Adrenal	1			1
Skin	5	1	3	1
Undifferentiated	14	9		5
Hodgkins' Disease	14	8	3	3

Table II continued.....

Lymphoma	25	15	9	1
Multiple Myeloma	15	10	2	3
Acute Myelogenous Leukemia	3	2		1
Acute Lymphocytic Leukemia	1		1	
Chronic Myelogenous Leukemia	8	7		1
Chronic Lymphocytic Leukemia	8	4	2	2
Fibrosarcoma	1	1		
Melano-Sarcoma	15	8	6	1
Osteogenic Sarcoma	6	1	1	4
Rhabdomyosarcoma	4		1	3
Liposarcoma	1	1		
Hemangioblastoma	1	1		
Histiocytoma	1			1
Brain Cancer	133	80	2	51
Retinoblastoma	1		1	
	500	247	86	167

Patients, Materials and Methods

Anti-Malignin Antibody Studies from Serum

Cancer patients were chosen by the clinical investigators at each of nine hospitals in the approximate frequency of their rate of occurrence in their population or according to the investigator's particular interests (see Table II). Untreated as well as treated cases were accepted. Of the 500 cancer sera studied, 247 (49.4%) were from patients who had clinically and pathologically assessed active disease with terminal cases excluded, 167 (33.4%) were from terminal patients only as defined by date of death within one year after the specimen was taken, and 86 (17.2%) were from those who had both clinically and pathologically defined and successfully treated cancer up to 15 years earlier and had no clinical or pathological evidence of disease at the time the antibody was determined (fourth control group, see below). Of the active cancer group, 76

patients could be followed who were still alive beyond one year and up to 46 months. Four control groups were studied: (1) 59 healthy normals (60 sera); (2) 56 hospital out-patients with some symptoms but without definite clinical diagnosis, no malignancy, or other major diseases (56 sera); (3) 258 hospital in-patients with definite medical-surgical diagnoses, but no malignancies (261 sera); and (4) the 86 cancer patients referred to above who had no evidence of disease at the time of the determination. The medical-surgical diagnoses in the third control group included bacterial infections (26 sera), viral infections (28 sera), trauma (8 sera), cardiovascular disorders (30 sera), gastrointestinal and hematopoietic disorders (39 sera), thoracic disorders (6 sera), obstetrical and gynecological disorders (7 sera), genitourinary disorders (11 sera), endocrine metabolic and arthritic disorders (22 sera), neurologic disorders (62 sera), psychiatric disorders (6 sera), and dermatologic disorders (16 sera). In addition to the above randomly collected sera, selective blind studies have been initiated but not completed on several specific groups: 45 patients with multiple sclerosis (49 sera) and 57 with benign tumors (74 sera), as well as on 31 blood relatives ('relatives') or cancer patients (31 sera), on people in contact with cancer patients, that is, 54 non-blood relatives and hospital staff ('contacts') (63 sera). 82% of the sera were from the Medical College of Ohio. The results in any of the hospitals did not differ from any of the others.

Malignin Studies of Cells

The presence of Malignin was sought in cells collected from patients at the Roswell Park Memorial Institute and examined at the Medical College of Ohio. Specimens were collected by thoracocentesis, paracentesis, bronchial or tracheal washings, from sputum and pericardial effusion, from patients with lung, breast, prostatic, colon and undifferentiated cancers, as well as from non-cancer controls including patients with emphysema, heavy smoking history, epilepsy, and sputum from a former cancer patient with no evidence of disease for two years following successful treatment.

Immunochemical Methods

Serum Antimalignin antibody was quantitatively determined by an immunoabsorption method previously described (Bogoch

and Bogoch, 1980a). The antibody is specifically adsorbed to immobilized Malignin polypeptide (Table 1) ('Target' reagent) in a 2-hour (slow) and a 10-minute (fast) reaction, then released in soluble form and read by optical density at 280 millimicrons as micrograms of antibody protein (Bogoch and Bogoch, 1980a). The existence of these two distinct species of the antibody has been recently confirmed by the *in vitro* production of a unique monoclonal antibody for each of the slow and the fast reacting forms (Bogoch, 1981). The values of Anti-malignin antibody in serum are expressed as net Target-attaching globulins ('Net TAG') calculated: 2-hour immunoadsorption [Slow (S) TAG] less the 10-minute immunoadsorption [Fast (F) TAG]. All vaues given represent Net TAG values unless otherwise noted. The Net TAG does not appropriately reflect the antibody elevation when the F-TAG is markedly elevated to between 270 and 1100 micrograms/ml. In these instances, seen rarely in the four control groups (2 of 464 sera, 0.4%), but in 58 of 247 active cancer sera (23.5%), the S-TAG values are also elevated to above 400 and as much as 1200 micrograms/ml. In the accompanying figures, to distinguish these cases of extraordinary increase in both forms of antibody, rather than adding the values for the two forms, only the S-TAG has been plotted as open circles. These cases have been examined statistically in two ways: separately, and as part of the clinically determined active cancer group. Malignin was detected in cells by a standard Coons double-layer immunofluorescent method previously described in which purified human Anti-malignin antibody ('MTAG' reagent) is the first layer and fluorescein bound to anti-human gamma globulin is the second layer (Bogoch, 1977; Harris *et al.*, 1980). The reagents were obtained from Brain Research, Inc., New York. Both methods were performed blind on coded specimens of sera and cells, respectively, by laboratory personnel who were in a different center than the one in which the specimens were collected.

Correlation of Clinical and Laboratory Data

Correlations were made for each patient after completion and recording of both clinical and laboratory data separately. The error for these correlations in terminal cases is likely to be very small since it involved pathologically confirmed cancer and two

reliable dates: the date of the antibody determination and the date of death. For each of 206 of the 247 active cancer cases, in addition to the absence of their names from the tumor registry of deaths, it was possible to verify by contacting each patient or their physician that the patient was still alive at the end of one year. For 41 of these cases, the contact verification either was not possible or possible only to the tenth month. Since most of these 41 cases were from the first two years of the study, when clinically terminal patients were actively excluded from the study, this is not likely to represent an appreciable error. At most, the number in the active cancer group would be reduced and the number in the terminal group increased, each by 41, neither of which would significantly influence the conclusions reached except for the value of the mean for the antibody in the terminal group which would be increased. In the statistical comparison of the groups, values of $p<0.01$ were considered statistically significant. The only comparison of those found not significant under these criteria which approached but did not quite reach the 0.05 level was between the first two control groups (Figure 1). A preliminary report was made on the first 290 specimens studied (Bogoch *et al.*, 1979).

Results

Figure 1 shows the concentration of Anti-malignin antibody, in micrograms/ml serum in individual sera, in the four control groups and the active cancer group: that is, (1) healthy normals, (2) cancer patients showing no evidence of disease after successful treatment, (3) out-patients (non-cancer) with medical-surgical symptoms but without defined disorders, (4) in-patients (non-cancer) with defined medical-surgical disorders, and (5) patients with active cancer who lived one year or longer. While the four control groups did not differ from each other at a statistically significant level, each differed from the active cancer group at the significant level of $p<0.000001$.

Figure 2A shows the concentration of Anti-malignin antibody in individual sera of patients with terminal cancer, that is, those who died within one year (mean 4.4 ± 3.5 months). The concentration of antibody in this group differs statistically from the active cancer group at a level of $p<0.000001$. Together with the data

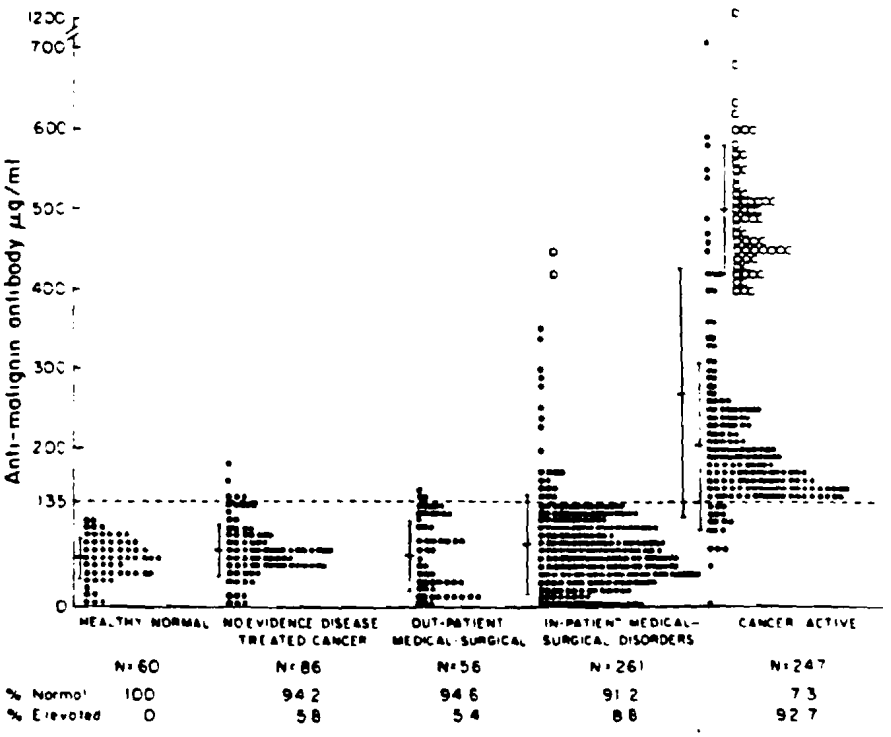


Figure 1.: Concentration of Anti-malignin antibody in four control groups and in active cancer patients. Solid circles, Net TAG; open circles, S-TAG (F-TAG excess). See Methods for details.

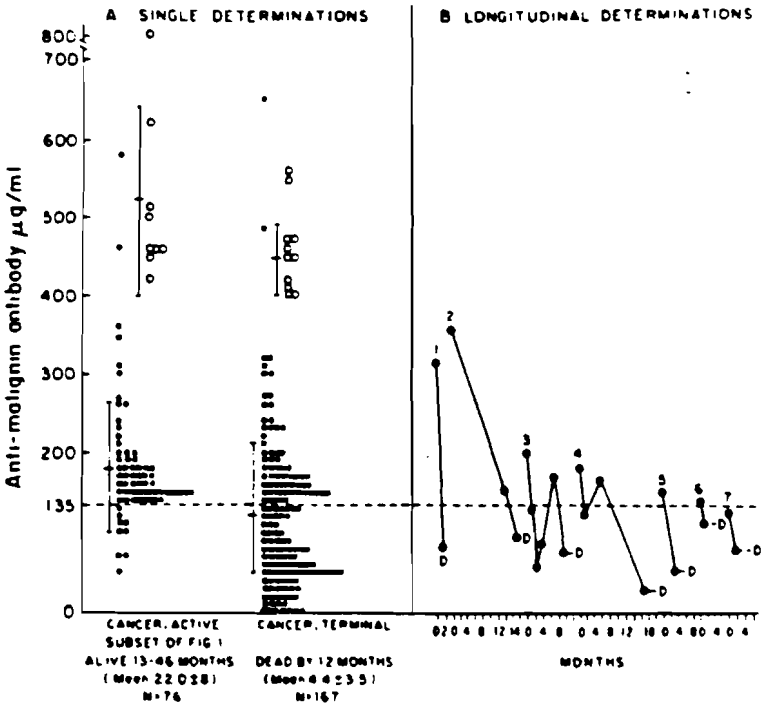


Figure 2.: Relation of level of Anti-malignin antibody to terminal clinical state. Solid circles, Net TAG; Open circles, S-TAG (F-TAG excess). See Methods for details. A. Single blind determinations in individual patients. B. Longitudinal blind determinations on seven individual cancer patients (1 through 7) whose death (D) occurred 1 to 4 months from the date the last specimen was determined.

TABLE III

		CELL MALIGNIN: IMMUNOFLUORESCENCE MTAG RESULTS		
		Cancer	*Non-Cancer*	*Total*
Clinical-Pathological Diagnosis	Cancer	14	2	16
	Non-Cancer	0	6	6
	TOTAL	14	8	22

shown in Figure 1, it may be seen that 90 of 108 cancer patients (83.3%) who had antibody levels below 135 micrograms/ml died within one year. In contrast, of the 76 active cancer patients who were longer term survivors and who could be followed 13 to 46 months (mean 22.3 $\pm$ 8) after the antibody determination, 68 (89.5%) had had elevated antibody levels. Figure 2B shows seven examples of the decrease before death observed in individual patient's serum Anti-malignin antibody levels when determined serially.

Table II shows the types of cancer patient studied, and the distribution of samples between active disease, terminal disease and no evidence of disease in each type of cancer. The distribution of type of cancer is fairly typical with the exception of an excess number of brain cancer cases which was the initial focus of interst of the study.

In the beginning blind study in each of the non-random pre-selected groups, the antibody level was elevated in the sera of 20.4% of patients with multiple sclerosis, 31.1% of patients with benign tumors, 30.2% of 'contacts' of active cancer patients, and 38.7% of blood relatives of active cancer patients.

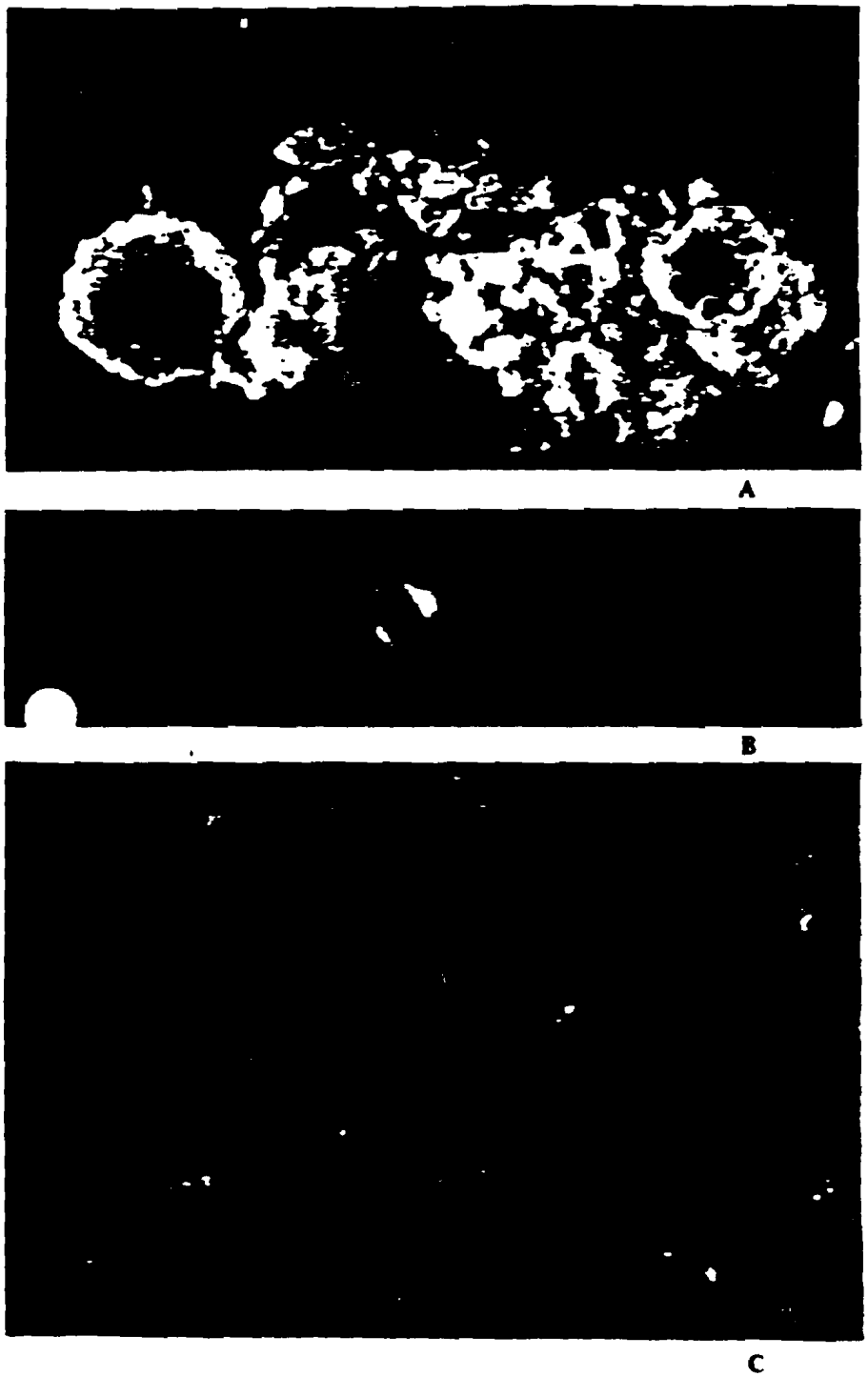
Table III shows the correlation of the presence or absence of Malignin in cells as determined blind by immunofluorescent staining with Anti-malignin antibody (MTAG), and the clinical-pathological diagnosis. The MTAG stain result was correct in 20/22 specimens (91%). Standard Papanicolaeu stain examinations performed blind on duplicates of these specimens by other pathologists were correct in 17/22 specimens (77%).

In addition to the positive stain for Malignin in cells from breast, ovarian and brochogenic carcinoma, and astrocytomas, cells grown in tissue culture from human squamous cell carcinoma of the vulva (Meck *et al.*, 1981), and from five different types of human lymphoma, as well as leukemic cells in both acute and chronic leukemia blood have demonstrated positive staining (Figure 3). Outer cell membranes as well as intracytoplasmic membranes are predominately stained, with sparing of the nucleus, in agreement with the localization of the Malignin antigen as determined by cell organelle fractionation and direct isolation. Non-neoplastic adult tissues (Harris *et al.*, 1980) and normal fetal tissues have been uniformly negative for Malignin except for two cases of astrocytosis.

Discussion

The data obtained in this blind study are consistent with the previous evidence that Malignin is a general transformation antigen. Thus, rather than being restricted to particular cell types, Anti-malignin antibody was elevated significantly above normal levels, and Malignin was visualized in cells, in patients with a broad variety of active cancer (Table II, Figure 3, and Immunochemical Methods). That the antibody was in the normal range in 94.2% of patients who had been sucessfully treated and at the time of the antibody determination showed no evidence of disease, suggests that an active cancer state is required to maintain elevated antibody levels. In the separation of healthy normal subjects from active cancer patients by determination of Anti-malignin antibody, all healthy normals had values below 135 (mean 59.1 $\pm$ 27.0) micrograms/ml and there were no 'false positves', while in the active cancer group, 92.7% showed elevated values of antibody (mean 273.7 $\pm$ 156.5 micrograms/ml). The healthy normal and the active cancer groups differed at a level of $p<0.000001$ for the whole active cancer group, as well as for each of the two subgroups shown in Figure 1.

As medically-ill subjects are brought into the comparison (Figure 1), the mean levels of concentration of antibody are seen to shift slightly but not significantly upward. In the out-patient non-cancer group, 94.6% were still in the normal range, and 5.4% were in the elevated range. In the in-patient, more clearly ill, positively



A

B

C

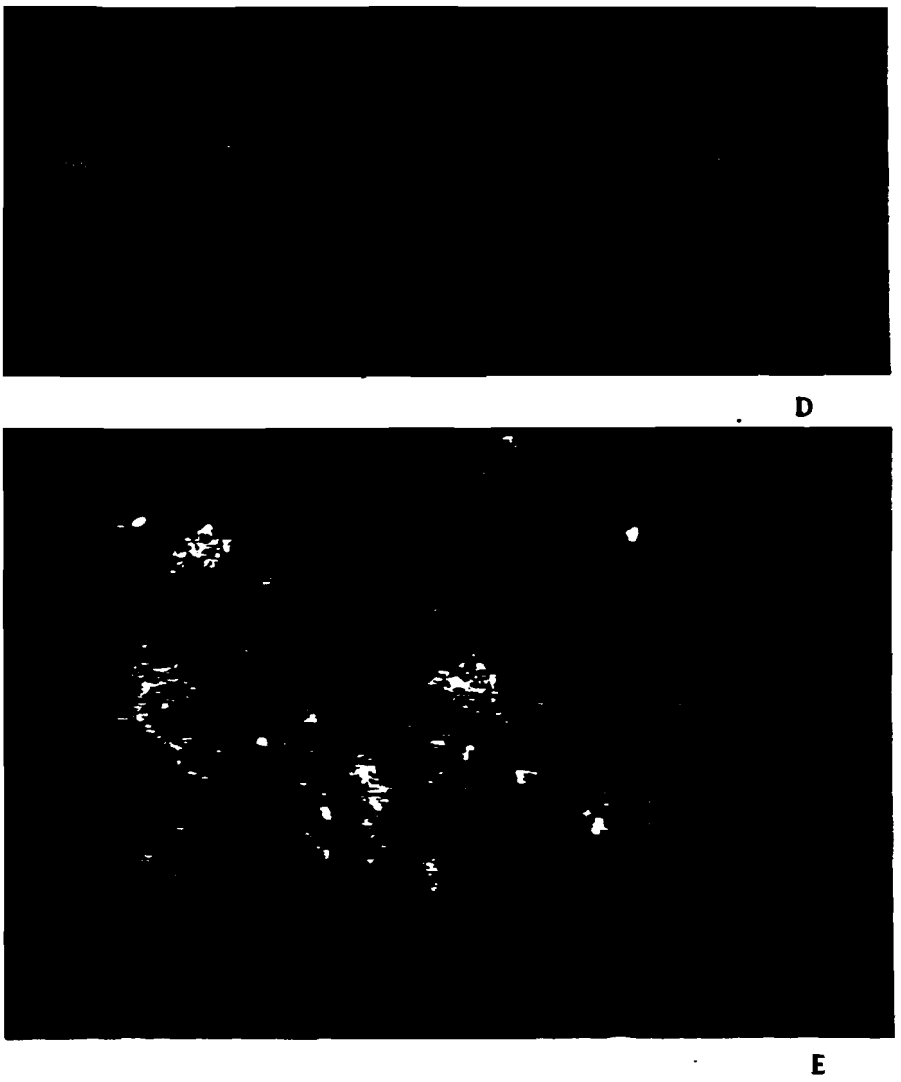


Figure 3.: Malignin visualized in a variety of human cancer cells by Anti-malignin antibody double-layer immunofluorescence. The second layer fluorescein labeled anti-antibody was diluted in control experiments to as much as 1:1,600 until non-specific fluorescence was completely eliminated in the absence of the first layer Anti-malignin antibody. Under these conditions, Anti-malignin antibody was active at one nanogram antibody protein per cancer cell in producing the specific immunofluorescence shown in the figure. A - Bronchogenic carcinoma cells from bronchial washings. B - Lymphocytic leukemia cell from blood. C - Ovarian carcinoma cells at surgery. D - Squamous cell carcinoma (2 cells), grown in tissue culture (Meck et al., 1981). E - Astrocytoma, anaplastic, at surgery. See Methods and Results for further details.

diagnosed (but apparently non-cancer) medical-surgical group, 91.2% were still in the normal range, and 8.8% were in the elevated range. These two control groups were not statistically significantly different from the healthy normal control group, but each differed from the active cancer group at a level of $p<0.000001$*. It might be expected that compared with healthy normals, the incidence of cancer would be greater in medically ill patients and that some of these cancer cases might not yet be clinically diagnosable. How many of these presumptive 'false postives' actually represent occult cancer not yet clinically detected cannot be predicted, but it is relevant to note that six additional 'false positives' were found from one to 19 months later actually to have clinically and pathologically proven cancer.

The data in the preselected groups, although blind, were not randomly collected as were those in Figures 1 and 2 and, therefore, cannot be pooled with them. Each of these preselected groups is considered too small to form conclusions because of heterogeneity of each and the complexity of the implications raised by the data, but they are included as preliminary data for the sake of completeness. There is a possibility that because of the destructive and immune reactions in the nervous system in multiple sclerosis a higher false positive rate may occur. Some of the cases may represent misdiagnosed central nervous system malignancy. Sera from patients with benign tumors might be expected to show a higher false positive rate consistent with the borderline area in clinico-pathological diagnosis between benign and malignant growths. Anti-malignin antibody levels and the demonstration of Malignin in cells may in the future help to clarify the definition in this group. The observation of higher incidence of elevated Anti-malignin antibody in contacts of active cancer patients (compared with healthy normals $p<0.001$) is in agreement with several previously published studies on other tumor indexes demonstrating the same curious phenomenon (14 clinical studies and one laboratory study) (Editorial, 1977). Whether this represents some form of immunization against a transmittable agent, either the Malignin antigen itself or a substance which induces transformation and, thus, the appearance of the antigen, needs more work to clarify. Finally, the greatest incidence of antibody elevation in a 'non-cancer' group is observed

*Confirmed independently with 360 additional cases by Dungan *et al.* (Unpublished).

in the blood relatives of active cancer patients. Whether this represents a response to actual cell transformation, a genetically determined high level of production of the antibody for immunosurveillance, or the same phenomenon as that observed in the 'contacts' group is unknown. Since the 'relatives' are statistically different from the healthy normal control group at a level of $p < 0.000001$, some explanation will have to be sought and certainly much larger groups will have to be examined.

The possible utility of the Malignin antigen and the antibody for general screening of populations for cancer is suggested by the 'false positive' rates shown in Figure 1 in the healthy normal and out-patient control groups. Further studies are now in progress. The results of the present studies present the possibility, within the limitations of all laboratory procedures, that both the determination in cells of Malignin and in serum of its antibody may be useful in helping to recognize the presence of malignant states in individuals in whom cancer is suspected. In addition, the clinical follow-up of individual patients over months and years has permitted the comparison of clinical outcome with antibody levels which were obtained on blind coded serum specimens. The correlation observed suggests that the Anti-malignin antibody level may be related to survival in that the elevated values during active disease were associated with longer survival and low levels during active disease with early death. After successful treatment, however, the presence of normal (low) antibody levels may be an aid in determining whether an active cancer state has been replaced by one in which there is 'no evidence of disease'. Once again, the laboratory value can have relevance only in relation to the clinical status, and it usually should not be difficult to separate the clinically healthy from the clinically terminal patient, both of whom have low levels of antibody, but for different reasons.

The significance of the correlation of lower levels of Anti-malignin antibody with terminal illness shown in Figures 2A and 2B is not known. Since as seen in Figure 2B, the drop in antibody can occur abruptly, in as little as one month before death, it is not known how many of the elevated values shown in Figure 2A were followed by a similar drop prior to death. The drop may, therefore, be even more common than observed in the single determination.

The phenomenon is in accord with previous demonstrations by others of the general decrease in immunocompetence observed to signal oncoming death in both human and animal cancer (Hersh *et al.*, 1976), and may simply represent a secondary consequence of the terminal state. However, since Anti-malignin antibody is specific for a cancer cell antigen, localizes preferentially in malignant cells *in vitro* and *in vivo*, and has been shown to be cytotoxic to malignant cells *in vitro* (Bogoch and Bogoch, 1980), the drop in antibody might be more central to the cancer process and be to the detriment of the patient. In addition, earlier data (Bogoch and Bogoch, 1979a) showed Anti-malignin antibody in human cancer sera to be largely 'disarmed', with its Fc portion cleaved from the Fab fragments, which would result in loss of cytotoxicity. This process might reflect one form of the cancer cell's defense eagainst the antibody. The low levels of antibody observed here prior to death may be evidence of a second form of the cancer cell's defense, the result of increasing blockade of antibody production or release due to antigen excess as the tumor proliferates.

That Malignin is not an 'onco-fetal' antigen is supported by the absence of Malignin from fetal tissues. Malignin appears to be much older phylogenetically than those states commonly thought of as being recapitulated during fetal development; its only structural relatives, by computer search (Dayhoff, 1972), are the ferrodoxins of plants (lucaena glauca and alfalfa), the acyl carrier protein of *E. coli*, and cytochrome b5. These four share the property of being anerobic enzymes, the ferrodoxins being the most electronegative oxidation-reduction enzymes in nature. Warburg *et al.* (1958) observed the anerobic advantage of malignant cells, but was unable to account for this property in the activity of the then known anaerobic enzymes. The possibility that Malignin is a cleaved derivative of such an anerobic enzyme system, that this system is common to all malignancies regardless of cell type, and that this system imparts a unique anaerobic advantage to cancer cells, would be consistent with the demonstrated increase in the yield of Malignin with increasing malignancy of cell growth (Bogoch, 1976, 1977), the ubiquity of distribution of the antigen, the cytotoxicity of the antibody and the antibody failure in the terminal state.

Recently, both the purified human polyclonal Anti-malignin antibody and the individual monoclonal antibody for each of the

fast and slow binding species of the antibody became available. The therapeutic possibilities raised by these observations for the antibody acting alone or as a carrier for anti-cancer drugs should be systematically examined.

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