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Tracheobronchial Epithelial Multinucleation in Malignant Disease

Abstract. *Multinucleated tracheobronchial ciliated epithelial cells seen in smears from 112 patients suffering from a wide variety of malignant tumors were found to be 2.08 times more numerous than in a control group comparable in sex, age (decades), and smoking habit but without prediagnosed malignancies. The recognition of this phenomenon may lead to the development of a new test for the diagnosis of occult cancer and may open new pathways for investigation of cancer-host relationships.*

In a series of ongoing studies we are conducting on the exfoliative cytology of the tracheobronchial tree of patients undergoing general endotracheal anesthesia for surgery, thus far totaling 2983 cases, it has become increasingly evident to us that the morphology of the ciliated epithelial cells was affected by a wide variety of stimuli (*1*). We also gained the impression that smears from patients suffering from known systemic malignancies contained unusually large numbers of multinucleated ciliated cells. We have, therefore, carried out a retrospective pilot study to ascertain the statistical significance of this phenomenon. The preliminary results of this effort have been sufficiently dramatic to warrant preliminary publication.

Smears known to have contained at least 200 ciliated cells from 112 patients suffering from malignant tumors were reviewed, and the percentage of noncancerous cells containing more than one nucleus was calculated in relation to the total number of ciliated cells seen in each smear. The maximum number of nuclei in any one cell per smear was also noted. A randomly selected control group of smears from patients without known malignancies, and matched exactly by decade of age, sex, and smoking habit (*2*), was retrieved from the files and similarly examined. No patient was included who had received chemotherapy with alkylating agents or immunosuppressive drugs, or treatment with ionizing radiations, for at least 2 years before the collection of the specimen, to avoid contamination of data by changes in tracheobronchial cytology due to the use of these agents (*3*). All smears had been made from secretions obtained by suction of the tracheal tube immediately after intubation. This material was spread on microscope slides, spray-fixed at once, and stained (Papanicolaou). Microscopic examination was carried out by two of us (J.C. and J.S.K.), each of whom was unaware of the origin of the smears which had been previously mixed and tagged by the other members of the study group. Mean scores of the readings of both observers were used for final analysis of data. The mean percentages of multinucleated cells and the standard errors of the means were then calculated for all malignant and control groups and for subgroups divided by age, sex, smoking habit, and site of origin of tumors. Student's *t*-test for uncorrelated series was used for statistical analysis. Statistical significance was selected at values of $P < .02$.

The mean percentages of multinucleated cells in smears from patients with malignant disease and for all controls (Table 1) were 3.93 ± 0.22 and 1.89 ± 0.11, respectively ($P < .001$). If cases were subdivided by age, sex, and smoking habit, the difference in percentage of multinucleated cells between tumor and control groups remained statistically significant ($P < .02$) in each group. The higher percentage of multinucleated cells in men with malignant tumors (4.24 ± 0.45) over those from women suffering from the disease (3.78 ± 0.27) was not significant, nor was the higher incidence of multinucleation seen in smears from very heavy smokers with malignant disease (4.96 ± 0.65) over the mean incidence of multinucleation in all other smoking groups (3.93 ± 0.24).

When mean percentages of multinucleation were studied by site of origin of tumors, all tumor groups containing at least nine cases (colon and

Table 1. Mean ($\bar{X}$) percentage of multinucleated cells in patients with tumors and in controls; S.E., standard error; N.S., not significant.

Group studied	Tumors			Controls		*P*
	N	$\bar{X}$	S.E.	$\bar{X}$	S.E.	
Total study	112	3.93	0.22	1.89	0.11	< .001
Males	36	4.24	.45	1.87	.19	< .01
Females	76	3.78	.27	1.90	.15	< .01
Age groups						
10 to 39	14	4.09	.63	2.01	.39	< .01
40 to 69	68	3.81	.27	1.86	.14	< .001
70 and over	30	4.11	.55	1.89	.24	< .01
Smoking habit						
Nonsmoker	62	3.88	.31	1.19	.15	< .01
Light smoker	10	3.86	.57	2.00	.41	< .02
Medium smoker	10	4.02	.83	1.87	.40	< .02
Heavy smoker	21	3.60	.60	1.79	.24	< .02
Very heavy smoker	9	4.96	.65	1.89	.62	< .01
Site of origin						
Colon and rectum	32	3.60	.35	2.06	.22	< .01
Breast	28	4.28	.45	1.95	.29	< .01
Female genital	18	3.95	.55	1.73	.25	< .01
Stomach	9	3.54	.59	1.75	.37	< .02
Miscellaneous	6	3.59	.49	1.25	.34	< .02
Other digestive	6	4.58	1.65	1.27	.12	N.S.
Urinary system	5	4.19	0.92	2.60	.27	N.S.
Lymphomas	4	3.62	1.66	1.33	.21	N.S.
Bronchogenic	4	4.47	1.66	2.5	1.20	N.S.

rectum, stomach, breast, and female genital) had degrees of multinucleation significantly higher than controls ($P < .02$). With the exception of a group containing six unrelated tumors, the mean degree of multinucleation in groups containing less than nine cases (urinary system, lymphomas, bronchogenic carcinomas, and digestive other than stomach, colon, and rectum), although comparatively as high as in all other groups, was not statistically significant. When the mean degree of multinucleation for all these small groups totaling 19 cases was calculated, it was found to be 4.25 ± 0.7 against 1.91 ± 0.3 for controls ($P < .01$).

When the percentage of smears falling into multinucleation groups rising by increments of 3 percentage points was calculated (Fig. 1), the majority of controls (83.9 percent) were found in the 0 to 2.99 percent multinucleation range and the majority of cancers (64.2 percent) above that range. There were always more cancers than controls when multinucleation exceeded 3 percent, and no control was found to have more than 6.25 percent multinucleated cells.

The mean high number of nuclei per cell per smear was 3.34 ± 0.15 for cases with tumors and 2.25 ± 0.08 for controls ($P < .01$).

Although significantly higher numbers of tracheobronchial ciliated multinucleated cells and a higher degree of multinucleation were found in patients with malignancies, and were not affected by sex, age, or smoking habit, it is impossible to foretell at present if this finding will remain consistent for all histological types of tumors when the series is expanded. A prospective multihospital study is under way.

Our findings are in accord with those of Persoglia and Maiolo (*4*), who found noncancerous multinucleated transitional epithelial cells in the urine of 21 cases of carcinoma of the cervix.

We cannot at present explain our results but can analyze them in relation to modern theories on the etiology of malignant disease. If human tumors are caused by viruses (*5*) it is possible that such viruses could cause multinucleation in distant epithelial tissues. Nowakovsky *et al.* (*6*) have already shown that the herpes simplex virus produces epithelial multinucleation not only in the original lesion but also in apparently unaffected tissues such as the transitional epithelium of the urinary collecting system.

According to Green, Bennett, Davidsohn, and Eilber and their co-workers (*7*), malignancy is associated with immunologic changes. It may be, therefore, that the phenomena we have described are related to disturbances in humoral activity in patients with cancer. Berkheiser (*8*) has shown that corticosteroids, which have a strong immunosuppressive action, produce hyperplasia of the tracheobronchial epithelium.

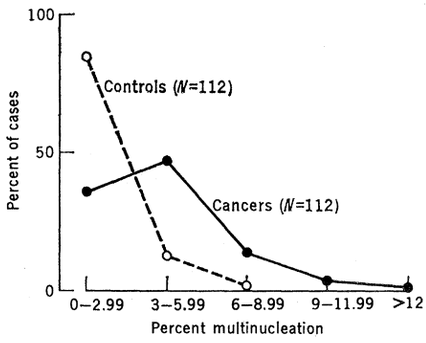

Fig. 1. Frequency distribution of multinucleated ciliated tracheobronchial epithelial cells in patients suffering from known malignancies, compared with a matched control group.

It may be that patients with carcinoma have an inherent tendency to multinucleated cells or their production by some invasive or inherent mechanism.

An important aspect of our study is the search for occult cancer in patients with high percentages of tracheobronchial epithelial multinucleation in the control group.

J. CHALON
J. S. KATZ
S. RAMANATHAN
M. AMBIAVAGAR, L. R. ORKIN
Anesthesiology Department,
Albert Einstein College of Medicine
of Yeshiva University,
Bronx, New York 10461

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Paradoxical Increase in Rate of Catabolism of Low-Density Lipoproteins after Hepatectomy

Abstract. *It has been suggested that the liver may be a major site for irreversible degradation of low-density lipoprotein (LDL). The disappearance of autologous ^{125}I-labeled LDL from plasma was compared in intact and in hepatectomized swine. Contrary to expectations, the rate of irreversible removal of LDL from plasma was increased rather then decreased by hepatectomy. These studies suggest that the liver is not a major site for LDL removal. We propose further that the liver (or some function requiring an intact liver) may affect the metabolism of LDL in a manner that prolongs its lifetime in the plasma compartment.*

Because the levels of low-density lipoprotein (LDL) in plasma are implicated in the pathogenesis of atherosclerosis, it is important to understand the mechanisms regulating LDL levels. It is generally accepted that the liver is the primary site of LDL biosynthesis although evidence for production of LDL apoprotein by the intestine has been reported (*1*). Very little is known about the sites or the mechanisms for LDL removal from plasma. Hotta and Chaikoff (*2*) reported that the rate of disappearance of labeled cholesterol from rat plasma was sharply reduced or arrested by hepatectomy. From this they concluded that the liver was the site of both the origin and the degradation of plasma lipoprotein cholesterol. Lewis *et al.* (*3*) reported a decrease in lipoprotein levels in hepatectomized dogs and suggested that there was some metabolism of lipoproteins in the periphery. Hay *et al.* (*4*), following the fate of [^{125}I]LDL, have suggested that in the rat the liver is a major site of LDL catabolism. We have previously shown that the major extravascular pool of LDL in swine lies in the liver (*5*). After injection of [^{125}I]LDL the liver