TECHNICAL PAPERS

Studies on Hypoproteinemia: III. Lymphoid Hyperplasia and Redistribution of Nitrogen Caused in Mice by Transplanted Tumors (Sarcoma 180 and Breast Adenocarcinoma EO 771)[1]

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Previous studies in patients with gastric cancer have shown that severe hypoproteinemia may persist for long periods of time while synthesis of tissue proteins takes place in the organism (*4*). A similar situation may be encountered in tuberculosis (*8*), in certain types of kidney disease (*5*), and in idiopathic hypoproteinemia or dysproteinemia (*3*). This phenomenon could be explained by either a selective defect of the synthesis of plasma proteins or by shunts of nitrogenous compounds away from the plasma into the proteins of other tissues.

The present preliminary report deals with a systemic effect of a transplanted tumor on the nitrogen metabolism of the mouse. It will be shown that in mice the implantation of sarcoma 180 causes hyperplasia of the lymph nodes with a significant shunting of nitrogen into the lymphoid tissue.

Groups of male CFW mice were pair fed, and sarcoma 180 was implanted into the right pectoral region of the animals of the experimental series. The tumors were allowed to grow for 6 days in one group and for 12 days in another. A third series was given implants of a murine adenocarcinoma of the breast (EO 771) that was allowed to grow for 12 days. A control group received no implants. At the end of the experiment the animals were killed by bleeding from the carotid artery.[3] The lymphoid system (thymus, two axillary nodes and mesenteric nodes) was dissected,[4] weighed immediately, and then homogenized in physiological saline solution for the determination of nitrogen by a micro-Kjeldahl method. The weight and the nitrogen content of the lymphoid tissue were expressed in mg/100 gm of body weight at the end of the experiment.

Table 1 shows that there was some loss of body weight in the control group, a more considerable loss in the group bearing sarcoma 180 for 6 days, and a slight rise in the group bearing the same tumor for 12 days. In contrast, there was a marked increase in weight of the lymphoid tissue in the mice with sarcoma 180, accompanied by a rise in nitrogen content of the lymphoid tissue. Implantation of a murine adenocarcinoma of the breast (EO 771) resulted in comparable increase in weight of the lymphoid tissue, accompanied by a rise in nitrogen content which was considerably smaller. Statistical analysis showed that these changes were definitely significant (Table 2). Histological studies showed that

TABLE 1

CHANGES IN BODY WEIGHT, WEIGHT OF LYMPHOID TISSUE, AND NITROGEN CONTENT OF LYMPHOID TISSUE IN MICE BEARING SARCOMA 180 AND IN MICE WITH TRANSPLANTED ADENOCARCINOMA OF THE BREAST (EO 771)

Type of tumor	Days of experiment	No. of animals	Body wt. (gm) before experiment	Body wt. (gm) after experiment	Change of wt. (%)	Lymphoid tissue wt. (mg/100 gm body wt.)	Increase over normal (%)	Lymphoid tissue nitrogen (mg/100 gm body wt.)	Increase over normal (%)
None (Control)	12	12	*27.7* (25.4–38.4)	*26.6* (24.8–32.8)	− 4	*287* (149–560)	...	*6.2* (1.7–13.6)	...
Sarcoma 180	6	12	*29.0* (23.9–36.6)	*25.0* (20.5–32.8)	−14	*779* (239–1,237)	+172	*23.9* (12.5–58.5)	+286
Sarcoma 180	12	12	*18.7* (12.8–24.0)	*19.5* (17.3–21.3)	+ 4	*588* (424–896)	+105	*14.2* (10.0–21.8)	+129
Breast tumor (EO 771)	12	12	.....	*23.7* (20.0–26.7)	..	*713* (500–1,070)	+148	*11.5* (6.8–18.8)	+ 85

The means are set in italic; the ranges are in parentheses.

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[3] This was necessary for the measurement of the plasma volume by the method of Furth and Sobel (*2*), which was done as part of a study on the general nitrogen distribution in blood, liver, spleen, carcass, tumor and lymphoid tissue of these animals, to be reported later.

[4] The lymphoid nature of the tissue studied was ascertained in some instances by histological examination.

the enlargement of the lymph nodes was due to simple hyperplasia and that there were no metastases. Details of this morphological study will be published later.

The interpretation of these findings must await the outcome of further analyses on the nitrogen content of other compartments in these animals. The relatively small increase in the nitrogen content of the lymphoid tissue of mice bearing adenocarcinoma of the breast suggests that in this case the lymphatic hyperplasia may be of a different nature than that observed in the mice bearing sarcoma 180.

The data of Murphy and Sturm (*6*) showed opposite trends in the weights of cervical lymph nodes of rats bearing a lymphosarcoma. This discrepancy of data obtained in different species emphasizes the complexity of the problem.

The findings of Savard (*7*) of adrenal hypertrophy in mice with sarcoma 180 and the parallelism between the observations of Dougherty and White (*1*) in adrenalectomized mice and our own data suggest the adrenal as a possible mediator of the phenomenon. However, other nutritional and hormonal factors must be investigated.

The experiments revealed a systemic effect on protein metabolism caused by transplanted tumors not usually considered to mediate endocrine mechanisms, and the observations may provide a new approach to the tumor-host relationship in animals and man.

TABLE 2

ANALYSIS OF VARIATIONS BETWEEN NORMAL AND TUMOR-BEARING MICE

	Mean	SEM	t value	P value
Nitrogen in lymph nodes and thymus (mg/100 gm body wt.)				
Normal	6.2	0.736		
Sarcoma 180 (6 day)	23.9	2.73	4.88	< .01
Sarcoma 180 (12 day)	14.2	0.87	5.54	< .01
Breast adenocarcinoma (EO 771)	11.5	0.82	3.74	< .01
Weight of lymph nodes and thymus (mg/100 gm body wt.)				
Normal	287	25.5		
Sarcoma 180 (6 day)	779	60.2	5.92	< .01
Sarcoma 180 (12 day)	588	22.9	5.61	< .01
Breast adenocarcinoma (EO 771)	713	28.3	7.55	< .01

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Zeeman Effect and *g*-Values for Neutral Nitrogen and Oxygen

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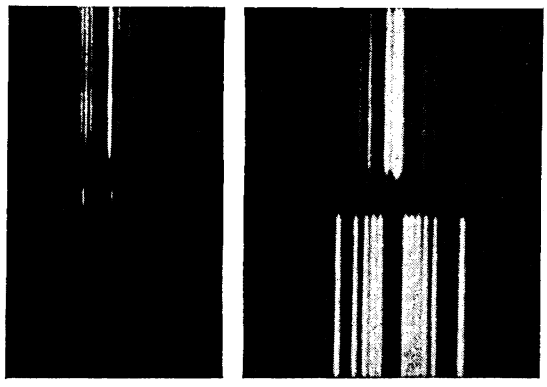
No *g*-values are available for the energy levels of atoms below 10, neon, except in the case of the ionized nitrogen and oxygen atoms. The reason for this is that the Zeeman patterns that have been reported are, for the most part, qualitative, or they are distorted. Recent Zeeman-effect observations of the red and infrared lines of various metals, made at the National Bureau of Standards and at the Massachusetts Institute of Technology, show the patterns of atmospheric nitrogen and oxygen lines as well. The nitrogen lines represent transitions from the terms $3p\ ^4D°$, $3p\ ^4P°$, and $3p\ ^4S°$ to the lower term $3s\ ^4P$, while those of oxygen result from transitions from $3p\ ^5P$ and $3p\ ^3P$ to $3s\ ^5S°$ and $3s\ ^3S°$, respectively.

On the spectrograms made at the National Bureau of Standards, with magnetic field-strengths of 35,000 gausses, and on the MIT spectrograms, with fields in excess of 85,000 gausses the nitrogen and oxygen Zeeman patterns exhibit various degrees of distortion both in the positions and in the intensities of the magnetic components. The nitrogen patterns exhibit only slight distortions or none at all. With the oxygen patterns the case is different: the quintet group, at 7,771–75 A, illustrated in Fig. 1, shows marked distortion at two different fields and bears no resemblance to either a weak-field pattern or to a Lorentz triplet; the triplet group, at 8,446 A, however, shows a nearly perfect Lorentz triplet pattern with very weak π-satellites also at the normal triplet separation.



A B

Fig. 1. Zeeman patterns of the oxygen lines at 7,771–74–75 A: A—34,660 gausses; B—85,400 gausses.

The interpretation of these patterns has afforded an interesting application of quantum theory to the elucidation of the Paschen-Back effect. Because the splitting of the atomic energy levels in the field is of the same order of magnitude as the level separations when no field is acting, it is found that the magnetic sub levels of the same