[CANCER RESEARCH 36, 3274-3278, September 1976]

Active T-Rosette-forming Cells in the Peripheral Blood of Cancer Patients[1]

Ronald H. Kerman, Randall Smith, Stefano S. Stefani, and Ediz Z. Ezdinli

Radiobiology Research Laboratory [R. H. K.] and Therapeutic Radiology Service [S. S. S.], Veterans Administration Hospital, Hines, Illinois 60141, and Departments of Medicine [R. S., E. Z. E.] and Radiotherapy [S. S. S.], Mount Sinai Medical Center/University of Health Sciences, Chicago Medical School, Chicago, Illinois 60612

SUMMARY

We studied a subpopulation of the thymus-dependent rosette-forming lymphocytes from the peripheral blood of normal individuals and of untreated patients with solid tumors or hematological cancers. This subpopulation of the thymus-dependent rosette-forming cells (T-RFC), termed the "active T-RFC," may be relatively more immunocompetent than the total thymus-dependent population. The mean percentages and absolute numbers of active T-RFC of 40 healthy adult controls were 25.8 ± 4.3 and 626 ± 213, respectively. There was no difference in the percentage of active T-RFC between the controls (smokers and nonsmokers) and the 102 untreated patients with solid (localized or metastasized) tumors, 4 patients with Hodgkin's disease, or the 10 patients with non-Hodgkin's lymphomas. However, the absolute number of active T-RFC was significantly less in the cancer patients than in the controls. Eight patients with chronic lymphocytic leukemia had lower percentages but higher absolute numbers of active T-RFC, whereas 6 patients with multiple myeloma had higher percentage and lower absolute numbers than the controls. Following radiation therapy, 61 patients with solid tumors showed no difference in the percentage of active T-RFC, but the corresponding absolute numbers declined significantly. A good correlation was seen with patients having positive microbial skin test responses and normal percentage of active T-RFC. The significance of both the percentages and absolute numbers of active T-RFC and their relationship to patient status are discussed.

INTRODUCTION

It is well established that human PBL[2] can bind with uncoated SRBC to form a characteristic rosette configuration (1). These RFC have been identified as T-lymphocytes (19). Two populations of T-RFC have been differentiated. The 1st population is called the total T-RFC and it was formed after a long incubation between PBL and SRBC, representing all T-cells in the peripheral blood; the 2nd population is called the active T-RFC and it was formed after a short incubation between PBL and SRBC, representing a subpopulation of the total T-RFC that may (*a*) have an active surveillance function, (*b*) be an index of cellular immunity, and (*c*) prove to describe the quality as well as the quantity of the immune responses (7, 9, 20).

Immune surveillance has been recognized as an important mechanism in the development of human cancer (3). The ability of the host to react against tumors was confirmed by experiments that showed that procedures impairing this mechanism enhance tumor progression (5, 6, 11). Previous studies suggested that (*a*) patients with malignant disease are immunologically compromised and (*b*) there is a close correlation between the degree of pretherapy immunocompetence and disease prognosis (8). It has recently been reported that cancer patients have decreased percentages of active T-RFC (21). Our own study indicated that patients with many different types of cancer have normal percentages of active T-RFC, but the absolute numbers are significantly lower than those of the controls. This difference between percentages and absolute numbers of RFC may delineate the problem of defining the quality or the quantity of the immune response.

MATERIALS AND METHODS

Patients. We studied 102 patients of both sexes with solid tumors (51 localized and 51 metastasized), 8 with CLL 6 with multiple myelomas, 4 with Hodgkin's disease (Stages IA, IIA, IIIB, and IVB), and 10 with non-Hodgkins's lymphomas (4 with Stage IV, 2 with Stage III, 1 with Stage II, 1 with Stage IIE, and 2 with Stage I). These 91 men and 39 women ranged in age from 24 to 73 years (mean, 50 years).

The solid tumors represented (*a*) 37 lung tumors (22 squamous cells, 6 undifferentiated, 4 oat cells, and 5 adenocarcinomas); (*b*) 36 head and neck carcinomas (3 of the nasopharynx, 4 of the floor of the mouth, 2 of the alveolar ridge, 3 of the tonsil, 4 of the larynx, 9 of the hypopharynx, 5 of the cervical esophagus, 2 neck lymph nodes with unknown primaries, and 4 of the tongue); and (*c*) 29 miscellaneous tumors (4 of the rectum-colon, 4 skin melanomas, 5 of the breast, 2 osteosarcomas, 1 of the uterus, 3 of the ovary, 1 mesothelioma, 2 renal cell carcinomas, 1 hepatoma, 2 of the prostate, 1 of the stomach, 1 of the pancreas, 1 of the bile duct, and 1 undifferentiated cancer). None of these patients had previously been treated by surgery, chemo-

[1] Supported by USPHS Grant CA14144-02, Goldblatt Brothers-Employees-Nathan Goldblatt Cancer Research Fund, Joel Greenberg Cancer Research Fund, and Veterans Administration Project 8121-08.

[2] The abbreviations used are: PBL, peripheral blood lymphocytes; SRBC, sheep red blood cells; RFC, rosette-forming cells; T-, thymus-dependent; T-RFC, thymus-dependent rosette-forming cells; CLL, chronic lymphocytic leukemia; Dulbecco's PBS, Dulbecco's phosphate-buffered saline.

Received February 18, 1976; accepted May 26, 1976.

Downloaded from http://aacrjournals.org/cancerres/article-pdf/36/9_Part_1/3274/2397516/cr0369p13274.pdf by guest on 03 August 2024

therapy, or radiotherapy. Fifty-eight patients with solid tumors were treated with radiation therapy; their active T-RFC were evaluated before and 30 days after completion of the therapy. Twenty-nine patients with carcinoma of the lung received an average of 4620 rads, and 29 patients with head and neck carcinomas received an average of 6164 rads of irradiation.

Controls. As controls we used 40 healthy adult men and 18 healthy adult women (hospital staff) ranging in age from 22 to 58 years (mean, 41.5 years). Thirty-two controls who had been smoking cigarettes on a daily basis were compared to 26 nonsmoker controls. None of the controls was known to have a disease that would affect their immune responsiveness.

Active T-RFC. Freshly drawn venous blood mixed with 20 units heparin per ml (Liquaemin Sodium 10; Organon, Inc., West Orange, N. J.) was layered onto Lymphoprep (Gallard-Schlesinger Chemical Mfg Corp., Long Island, N.Y.) (2) and was centrifuged at room temperature for 40 min at 400 × *g*. The monocytic cells (88 to 95% PBL) were carefully pipetted from the interface, washed 3 times in Dulbecco's PBS (pH 7.3), and brought to a final concentration of 2×10^6 PBL/ml in Dulbecco's PBS.

The SRBC, stored in Alvesar's solution (1:1) at 4° for no more than 7 to 10 days, were washed 2 times before being used and were adjusted to a 0.5% suspension in Dulbecco's PBS.

For measuring the active T-RFC we used our modification, reported earlier (13), of the procedure of Wybran *et al.* (18). Briefly, 0.25 ml (5×10^5) of PBL was mixed with 0.25 ml of 0.5% unsensitized SRBC and was centrifuged immediately at room temperature for 5 min at 200 × *g*. The cell pellets were gently resuspended and a drop of the suspension was placed onto a hemocytometer and the number of active T-RFC (3 or more SRBC surrounding a lymphocyte) were counted. All tests were performed in duplicate and 200 or more PBL were counted to determine the percentage of active T-RFC. The absolute numbers of active T-RFC were determined by calculation of the corresponding total and differential leukocyte counts. The results are reported as the mean percentage or absolute number/cu mm of active T-RFC ± 1 S.D. The statistical differences of the patient groups studied compared with controls were determined by Student's *t* test.

The technicians counting rosettes were not told whether the samples came from patients or controls.

Skin Test Antigen Response. The antigens used were: dermatophytin (1:30), dermatophytin-0 (1:100) (Hollister-Steir Labs, San Leandro, Calif.), streptokinase-streptodornase (50 units streptokinase) (Lederle Labs, Pearl River, N. Y.), mumps (Eli Lilly & Co., Indianapolis, Ind.), and intermediate-strength tuberculin antigen (Parke, Davis & Co., Detroit, Mich.). All were applied by intradermal inoculation in a volume of 0.1 ml through a 27-gauge needle. We observed the reaction at 24 and 48 hr and recorded the average in mm of the indurations measured at 2 right angles. Induration greater than 5 mm was considered positive and patients were considered positive responders if they reacted positively to 2 or more of the 5 antigens.

Table 1

Active T-RFC of selected cancer patients: comparison of the procedures of Smith et al. (13) and Wybran et al. (18)

Type of tumor	% active T-RFC	
	Procedure of Smith *et al.*	Procedure of Wybran *et al.*
Colon	43.0	42.0
Lymphoma	23.5	19.5
Lung	27.5	31.0
Lung	18.5	19.5
Breast	28.0	30.0
Breast	21.5	20.5
Breast	27.5	32.5
Breast	18.5	17.0
Melanoma	24.0	23.5
Prostate	19.0	18.0
CLL	8.5	7.0
CLL	5.5	6.5
Stomach	26.0	24.5
Bladder	19.5	24.0
Myeloma	31.0	34.0
Sarcoma	29.0	27.0
Uterus	18.5	17.0
Glioblastoma	23.0	22.5

RESULTS

In a previous study using a modified procedure for active T-RFC (13), we found that the percentage of active T-RFC of the controls was comparable to control values originally reported by Wybran *et al.* (18). Table 1 compares the active T-RFC of cancer patients measured by the 2 different procedures, Smith *et al.* (13) *versus* Wybran *et al.* (18). Clearly, both procedures produced similar results.

The mean percentage of active T-RFC for 58 controls was 25.8 ± 4.3 (mean ± S.D.); their absolute number was 626 ± 213. No difference was found in either the percentage or absolute number of active T-RFC when smokers were compared with nonsmoker controls (Table 2).

Before treatment, all our patients with newly diagnosed, solid tumors (as described in "Materials and Methods"), whether they had localized or metastatic disease, had normal percentages of active T-RFC. However, their absolute numbers of active T-RFC were significantly lower ($p < 0.001$) than those of the controls (Table 2). The site of the tumor did not significantly affect these numbers.

Data for patients with hematological cancers are seen in Table 3. Patients with CLL had lower percentages ($p < 0.001$) but greater absolute numbers ($p < 0.05$) of active T-RFC than did the controls. Those with multiple myeloma had higher percentages ($p < 0.05$) but lower absolute numbers ($p < 0.001$) than the controls. Patients with Hodgkin's disease and non-Hodgkin's lymphomas had normal percentages, but lower than normal absolute numbers ($p < 0.025$). There was no difference between the absolute numbers in patients with multiple myeloma, Hodgkin's disease, and non-Hodgkin's lymphomas. However, the absolute numbers for CLL patients were higher than those for the other hematological cancers as well as those for the controls.

Patients with solid tumors treated by radiation therapy showed no significant differences from controls in the percentage of active T-RFC, regardless of whether they were

Downloaded from http://aacrjournals.org/cancerres/article-pdf/36/9_Part_1/3274/2397516/cr0369p13274.pdf by guest on 03 August 2024

taken from cases with localized or metastasized tumors, before or 30 days after radiotherapy (Table 4). As mentioned before, the pretherapy absolute numbers of active T-RFC of patients with solid tumors were lower than those of controls (Table 2). Following radiotherapy, the absolute numbers of active T-RFC declined even further, so that they were significantly lower than pretherapy ($p < 0.05$) and control values as well (Table 4).

Correlation of the pretherapy percentage of active T-RFC and skin test responses for 58 patients with solid tumors is shown in Table 5. We found that 64% (37 of 58) of the patients had a normal percentage of active T-RFC and 55% (32 of 58) were positive responders to 2 of 5 or more skin test antigens. Seventy-six % (28 of 37) of those patients with normal percentages of active T-RFC were also positive responders to skin test antigens.

Table 2
Active T-RFC in controls and in patients with solid tumors

	No.	% active T-RFC	Absolute no./cu mm active T-RFC
Controls	58	25.8 ± 4.3[a]	626 ± 213
Smokers	32	26.4 ± 5.8[b]	653 ± 203[b]
Nonsmokers	26	25.2 ± 6.0[b]	594 ± 263[b]
Lung carcinoma	37	26.6 ± 11.0[b]	344 ± 246[c]
Localized	17	25.9 ± 7.7[b]	369 ± 262[c]
Metastatic	20	27.1 ± 13.4[b]	317 ± 233[c]
Head and neck carcinoma	36	23.9 ± 10.2[b]	404 ± 263[c]
Localized	30	23.9 ± 10.0[b]	452 ± 253[c]
Metastatic	6	24.1 ± 10.7[b]	317 ± 207[c]
Miscellaneous tumors	29	28.2 ± 10.9[b]	402 ± 242[c]
Localized	4	24.9 ± 16.7[b]	332 ± 190[c]
Metastatic	25	28.7 ± 10.1[b]	413 ± 250[c]

[a] Mean ± S.D.
[b] Not significantly different from controls.
[c] Significantly different ($P > 0.001$) from controls.

DISCUSSION

This report describes a study of the active T-RFC, a subpopulation of the total T-RFC, in normal individuals (smokers and nonsmokers), in pretherapy patients with solid tu-

Table 5
Correlation of pretherapy percentage of active T-RFC and microbial skin test response in patients with solid tumors

Patients with		
Normal % active T-RFC[a]	Positive skin test response[b]	Normal % active T-RFC and positive skin test response
37/58 (64)[c]	32/58 (55)	28/37 (76)

[a] Mean percentage of active T-RFC of normal controls ± 2 S.D.
[b] Positive response to 2 of 5 or more microbial test antigens.
[c] Numbers in parentheses, percentages.

Table 3
Active T-RFC in controls and in patients with hematological cancers

	No.	% active T-RFC	p	Absolute no./cu mm active T-RFC	p
Controls	58	25.8 ± 4.3[a]		626 ± 213	
CLL	8	14.4 ± 10.1	<0.001[b]	1674 ± 2022	<0.01[b]
Multiple myeloma	6	30.7 ± 8.4	<0.05[b]	338 ± 117	<0.001[b]
Hodgkin's disease	4	29.2 ± 9.8	NS[c]	359 ± 303	<0.025[b]
Non-Hodgkin's lymphomas	10	28.0 ± 11.3	NS	379 ± 208	<0.025[b]

[a] Mean ± S.D.
[b] Significantly different from controls.
[c] NS, not significantly different from controls.

Table 4
Active T-RFC in controls and in solid tumor patients treated by radiation therapy

	No.	% active T-RFC	Absolute no./cu mm active T-RFC	p
Controls	58	25.8 ± 4.3[a]	626 ± 213	
Carcinoma of the lung				
Localized disease	13			
Pre-RT[b]		27.4 ± 8.0[c]	450 ± 267	<0.01[d]
30 days post-RT		25.5 ± 11.0[c]	277 ± 107	<0.001[d]
Metastatic disease	16			
Pre-RT		24.8 ± 10.3[c]	293 ± 127	<0.001[d]
30 days post-RT		23.0 ± 9.4[c]	159 ± 82	<0.001[d]
Carcinoma of the head and neck				
Localized disease	29			
Pre-RT		24.5 ± 10.6[c]	416 ± 274	<0.01[d]
Post-RT		21.6 ± 7.4[c]	212 ± 130	<0.001[d]

[a] Mean ± 1 S.D.
[b] Pre-RT, preradiotherapy; post-RT, postradiotherapy.
[c] Not significantly different from controls.
[d] Significantly different from controls.

Downloaded from http://aacrjournals.org/cancerres/article-pdf/36/9_Part_1/3274/2397516/cr0369p13274.pdf by guest on 03 August 2024

mors or hematological cancers, and in patients with solid tumors postradiotherapy. We found no difference in the percentages or absolute numbers of active T-RFC for smokers or nonsmoker controls. Our study showed that untreated patients with these different cancers had normal or higher than normal percentages of active T-RFC but had below control values for the absolute numbers of these RFC (Tables 2 and 3). The only exception was represented by the 8 CLL patients studied who had significantly lower percentages and higher absolute numbers of active T-RFC than did the controls. This is in agreement with other reports (4, 21).

These results are in contrast to those recently reported by Wybran *et al*. (21), who found in patients with solid tumors, either localized or metastatic, primary or recurrent, lower than normal percentages of active T-RFC. Only patients in remission or those who had been treated successfully showed normal values. Early studies by Wybran *et al*. (18) of the active T-RFC in adults showed that the percentage of active T-RFC was increased in the presence of serum. Our technique, which is easier to perform and highly reproducible, eliminates the need for preincubation of PBL and the use of serum, while retaining the ability to identify active T-RFC (13). Furthermore, we have now shown that this modified procedure gives comparable results (Table 1) and thus measures the same population of active T-RFC of cancer patients as does that of Wybran *et al*. (18). It is therefore difficult at present to explain the differences in the 2 studies. Fudenberg *et al*. (7) have suggested that only some SRBC are able to discriminate cancer lymphocytes whereas others do not. We have studied the use of SRBC from various sources and have not found this to be a problem. It may be misleading to report only percentages or absolute numbers of RFC; both values should be reported, as both may be necessary to understand and interpret patient immune status (9).

Radiation therapy did not affect the percentage, whereas the absolute numbers of active T-RFC were significantly lower 30 days after therapy in patients with solid tumors (Table 4). Stratton *et al*. (17) recently reported that radiation therapy to either the mediastinum or the pelvis caused a rapid decrease in the absolute numbers of active T-RFC with a substantial recovery apparent 3 weeks after completion of therapy. No mention was made, however, of the effect of radiotherapy on the percentage of active T-RFC.

In a recent report (9) concerning the serial evaluation of the immune competence of transplant patients, known immunosuppressive measures, such as general surgery or pretransplant splenectomy or drug-induced immunosupression, did not affect the percentage, whereas the absolute numbers of active T-RFC were significantly decreased.

Several investigators have already reported the decrease in both the percentages and absolute numbers of the total T-RFC during surgery (12) or radiotherapy (14, 16, 17). These data indicate a disparity between the results of immune competence measured by (*a*) the active and total T-RFC and (*b*) the absolute number and the percentage of RFC.

The active T-RFC has been proposed to reflect better and to correlate with cell-mediated immune functions (20). If the active T-RFC possesses this property, it may reflect the quality as well as the quantity of the immune response (9). Patients treated with *Bacillus Calmette-Guérin* or transfer factor had increased percentages of active T-RFC, often with no change in the percentage of the total T-RFC (7). A drop in the percentage of active T-RFC preceded clinical, radiological, or chemical evidence of metastases in certain patients whose primary tumors had been removed (10). Decreases in the percentage of the active T-RFC but not in the percentage of total T-RFC have been correlated with clinical rejection episodes experienced by renal transplant recipients (9). These data seem to agree with the proposition that the active T-RFC is a surveillance cell.

A good correlation was seen between those patients with normal percentages of active T-RFC and positive responsiveness to microbial skin test antigens. We have previously reported a significantly lower level of the total T-RFC in these patients (14, 15). The results of this study may suggest that while patients have quantitatively few cells (decreased absolute numbers of active T-RFC), those existing lymphocytes may still possess immunological competence as evidenced by the normal percentage of active T-RFC and positive delayed hypersensitive responsiveness.

Evaluation of both the percentages and absolute numbers of the total and active T-RFC is important. However, the absolute number may only reflect the presence without indicating the quality of immune competence of existing lymphocytes. Measurement of the percentage of active T-RFC may prove to be a sensitive indicator of an immunocompetent T-cell. Studies of transplant recipients (9) and some cancer patients (10) suggest a direct correlation between the percentage of active T-RFC and patient status.

ACKNOWLEDGMENTS

We gratefully acknowledge the technical assistance of Linda Lave, Karen Maigetten, and Barbara Kase.

REFERENCES

1. Aitui, F., Cerottini, J-C., Coombs, R. R. A., Cooper, M., Dickler, H. B., Froland, S., Fudenberg, H. H., Greaves, M. F., Grey, H. M. Kunkel, H. G., Natvig, J., Preud'homme, J-L., Rabellino, E., Ritts, R. E., Rowe, D. S., Seligmann, M., Siegal, F. P., Stjernsward, J., Terry, W. D., and Wybran, J. Identification, Enumeration and Isolation of B and T Lymphocytes from Human Peripheral Blood. Clin. Immunol. Immunopathol., *3:* 584–597, 1975.
2. Boyum, A. Separation of Leucocytes from Blood and Bone Marrow. Scand. J. Clin. Lab. Invest., *21* (Suppl. 97): 77–89, 1968.
3. Burnet, F. M. The Concept of Immunological Surveillance. Progr. Exptl. Tumor Res., *13:* 1–27, 1970.
4. Catovsky, D., Miliani, E., Okas, A., and Galton, D. A. G. Significance of T-Cells in Chronic Lymphocytic Leukemia. Lancet, *2:* 751–752, 1974.
5. Chassot, P. B., Guttman, R. D., Beaudoin, J. G., Morehouse, D. D., Gonda, A., and MacLean, L. D. Cancer In Renal Allograft Recipients. Progr. Exptl. Tumor Res., *19:* 91–101, 1974.
6. Fisher, J. C., Davis, R. C., and Mannick, J. A. The Effects of Immunosuppression on the Induction and Immunogenicity of Chemically Induced Sarcomas. Surgery, *68:* 150–157, 1970.
7. Fudenberg, H. H., Wybran, J., and Robbins, D. T-Rosette-forming Cells, Cellular Immunity and Cancer. New Engl. J. Med., *292:* 475–476, 1975.
8. Hersh, E. M., Freireich, E. J., McCredie, K. B., Gutterman, J. U., Bodey, G. P., Whitecar, J. P., Mavligit, G., and Cheema, A. R. Primary and Secondary Immune Responses in the Evaluation of Immunocompetence and Prognosis in Cancer Patients. Recent Results Cancer Res., *47:* 25–36, 1974.
9. Kerman, R. H., Stefani, S. S., and Geis, W. P. Total and Active T-Cell Dynamics in Renal Allograft Recipients. Surgery, *79:* 398–407, 1976.
10. Levin, A. S., Byers, V. S., Fudenberg, H. H., Wybran, J., Hackett, A. J.,

Downloaded from http://aacrjournals.org/cancerres/article-pdf/36/9_Part_1/3274/2397516/cr0369p13274.pdf by guest on 03 August 2024

Johnston, J. D., and Spitter, L. E. Osteogenic Sarcoma: Immunologic Parameters before and during Immunotherapy with Tumor Specific Transfer Factor. J. Clin. Invest., *55:* 487–499, 1975.
11. Penn, I. The Incidence of Malignancies in Transplant Recipients. Transplant. Proc., *7:* 323–326, 1975.
12. Slade, M. S., Greenberg, L. J., Yunis, E. J., and Simmons, R. L. Integrated Immune Response to Standard Major Surgical Trauma in Normal Patients. Surg. Forum, *25:* 425–427, 1974.
13. Smith, R. A., Kerman, R., Ezdinli, E., and Stefani, S. A Modified Assay for the Detection of Human Adult Rosette Forming Lymphocytes. J. Immunol. Methods, *8:* 175–184, 1975.
14. Stefani, S. S., Kerman, R., and Abbate, J. Serial Studies of Immunocompetence in Head and Neck Cancer Patients Undergoing Radiotherapy. Am. J. Roentgenol., *126:* 880–886, 1976.
15. Stefani, S. S., Kerman, R., and Abbate, J. Immune Evaluation of Lung Cancer Patients Undergoing Radiation Therapy. Cancer, *37:* 2792–2796, 1976.
16. Stjernsward, J., Jondal, M., Vanky, F., Wigzell, H., and Sealy, R. Lymphopenia and Change in Distribution of Human B and T Lymphocytes in Peripheral Blood Induced by Irradiation for Mammary Carcinoma. Lancet, *1:* 1352–1365, 1972.
17. Stratton, J. A., Byfield, P. E., Byfield, J. E., Small, R. C., Benfield, J., and Pilch, Y. A Comparison of the Acute Effects of Radiation Therapy Including or Excluding the Thymus, on the Lymphocyte Subpopulations of Cancer Patients. J. Clin. Invest., *56:* 88–97, 1975.
18. Wybran, J., Carr, M. C., and Fudenberg, H. H. Effect of Serum on Human Rosette-forming Cells in Fetuses and Adult Blood. Clin. Immunol. Immunopathol., *1:* 408–413, 1973.
19. Wybran, J., and Fudenberg, H. H. Rosette Formation, a Test for Cellular Immunity. Trans. Assoc. Am. Physicians, *84:* 239–247, 1971.
20. Wybran, J., and Fudenberg, H. H. Thumus-Derived Rosette Forming Cells. New Engl. J. Med., *288:* 1072–1073, 1973.
21. Wybran, J., and Fudenberg, H. H. Thymus-Derived Rosette Forming Cells in Various Human Disease States: Cancer, Lymphoma, Bacterial and Viral Infections, and Other Diseases. J. Clin. Invest., *52:* 1026–1032, 1973.

Downloaded from http://aacrjournals.org/cancerres/article-pdf/36/9_Part_1/3274/2397516/cr0369p13274.pdf by guest on 03 August 2024