PERIPHERAL BLOOD Ia-POSITIVE T CELLS

Increases in Certain Diseases and after Immunization*

By D. T. Y. YU, R. J. WINCHESTER, S. M. FU, A. GIBOFSKY, H. S. KO, and H. G. KUNKEL

From The Rockefeller University, New York 10021

The human Ia antigens, products of the genes of the major histocompatibility complex, were first recognized primarily on the B lymphocytes by alloantisera obtained from pregnant or transplant subjects (1, 2). Heteroantisera were subsequently prepared by immunizing rabbits with highly purified antigens from solubilized membrane fractions of B-lymphoblastoid cell-line cells (3, 4). With the use of these antisera, it became apparent that a very small but definite percentage of peripheral blood T lymphocytes express such antigens (5). During the study, a few patients with elevated levels were also encountered. In addition, considerable elevations of the percentages of Ia^+ T cells have been found after stimulation with mitogens or during mixed leukocyte culture (MLC)[1] reaction (6–8). Patients with infectious mononucleosis (9) and graft-vs.-host reaction (10) also have been reported to show elevated levels of Ia-positive T cells.

In this study a broader examination of the Ia marker on T lymphocytes of patients with various diseases was made, employing both the allo- and heteroantisera as well as mouse monoclonal antibodies to Ia determinants. Special efforts were directed towards gaining an understanding of the significance of the elevations observed.

Materials and Methods

Patient Selection. Patients were selected from the clinics and wards of the Rockefeller Hospital, Hospital for Special Surgery, New York Hospital, and Memorial Hospital (New York).

Isolation of T Lymphocytes. Peripheral blood mononuclear cells were separated from heparinized blood samples by Ficoll (Pharmacia Fine Chemicals, Inc., Piscataway, N. J.) -Hypaque (Winthrop Laboratories, New York) gradients. T lymphocytes were isolated by rosetting these mononuclear cells with neuraminidase-treated sheep erythrocytes (RBC). The lymphocytes in these preparations usually consisted of 98% sheep RBC rosette-forming cells (RFC) and <2% surface Ig-bearing cells. They were designated as T preparations. Details of these procedures have been reported previously (5).

Surface Staining with Immunofluorescent Reagents. The rabbit anti-Ia antiserum used was the same and previously characterized as being highly specific for the broad group of Ia antigens (4). It was conjugated with rhodamine and absorbed with Ia-negative T-lymphoblastoid cell-line cells. Direct immunofluorescent staining was carried out using $F(ab')^2$ fragments as described previously (5). As noted in the previous study, the Ia^+ T lymphocytes in the

* Supported by U. S. Public Health Services grants AM04761 and RR 102, and by Rockefeller Foundation grant RF 70095.

[1] *Abbreviations used in this paper:* MLC, mixed leukocyte culture; PBS, phosphate-buffered saline; PPD, purified protein derivative(s); RBC, erythrocyte(s); RFC, rosette-forming cells.

preparations could be distinguished from the small numbers of contaminating monocytes by the weaker intensity of the fluorescence. In addition, double marker analyses, as shown previously (5), demonstrated that these cells formed rosettes with SRBC. The number of this type of positive cells was expressed as a percentage of the T-lymphocyte preparations.

To assess the allospecificities, the cells were first incubated with rabbit Cohn fraction II heat aggregated at 10 mg/ml in phosphate-buffered saline (PBS) at 63°C for 10 min, then with type-specific alloantisera, and, lastly, after three washings with PBS-1% bovine serum albumin, with rhodamine-conjugated goat antibodies directed against the Fc portions of human immunoglobulins (1).

To obtain Ia specific monoclonal antibodies, spleen cells from mice immunized with a B-lymphoblastoid cell line were fused with a mouse myeloma cell line (11). The antibodies secreted by one of these continuous cell lines were shown to react with the typical 28,000- and 37,000-dalton Ia components and to show a general specificity similar to the heteroantiserum. Lymphocytes were stained by reacting first with these antibodies at room temperature for 30 min and subsequently with a preparation of rhodamine-conjugated sheep anti-mouse Ig antibodies.

Indirect Rosette Assay. Isolated sheep anti-rabbit Ig antibodies (12) were coupled to bovine RBC by the chromium chloride method (13), resuspended in RPMI (Grand Island Biological Co., Grand Island, N. Y.) -10% fetal calf sera and kept at 4°C. The rosette assay was carried out in microtitre plates (Cooke Engineering Co., Alexandria, Va.). To each well of the plate was aliquoted 20 μl of lymphocytes at 10×10^6/ml in RPMI and 20 μl of optimum dilution of the rabbit anti-Ia antiserum. After 30 min of room temperature incubation, the cells were washed five times with PBS. After the last wash, 40 μl of a 2% suspension of the sensitized RBC were added to each well. The plates were centrifuged at 300 *g* for 5 min and kept at 4°C for 60 min. 10 μl of 1.0% toluidine blue were pipetted to each well and the cells vigorously resuspended by Pasteur pipettes. The percentages of RFC were determined by microscopic examination of 200 cells. Control samples were carried out in parallel in which a normal rabbit serum was substituted for the rabbit anti-Ia antiserum.

Autoradiography. Cytocentrifuge slide preparations of lymphocytes that had been labeled by a brief incubation with tritiated thymidine were coated with NTB2 emulsion (Eastman Kodak Co., Rochester, N. Y.) and stored in the dark for 2 d. After developing and fixing, the cells were stained with Giemsa stains. Positively labeled cells showed >5 grains/cell.

In Vivo Immunization with Tetanus Toxoid and Purified Protein Derivatives. Five normal subjects were given 0.5 ml of tetanus toxoid (The Upjohn Co., Kalamazoo, Mich.) subcutaneously. One other subject received an intracutaneous injection of 0.1 ml of purified protein derivatives of tubercle bacilli (Parke, Davis & Co., Detroit, Mich.). 10-ml samples of peripheral blood were collected before the immunization and at various days afterwards. All venipunctures were carried out between 8:00 and 9:00 a.m.

In Vitro Lymphocyte Culture. T lymphocytes obtained as described above were mixed with irradiated autologous monocytes at a ratio of 9:1. The latter were isolated by centrifugation of peripheral blood mononuclear cells on bovine serum albumin solution of density 1.386 g/ml. These cells were cultured at 1.5×10^6 cells/ml in RPMI-10% AB sera with 0.04 mg/ml of tetanus toxoid in a 37°C 5% CO_2 incubator. Aliquots were harvested every day for the immunofluorescent study. Because the monocytes adhered to the plastic surfaces of the culture plates (Linbro 76-033-05, Linbro Chemical Co., Hamden, Conn.), they constituted <2% of the cells in the harvested samples, as identified by cytocentrifuge preparations.

Results

Levels in Various Diseases as Compared with Normals

NORMAL SUBJECTS. The percentages of Ia^+ T cells in the peripheral blood lymphocyte preparations of 12 normal male and 12 normal female volunteers ranged from 0 to 4.8% by fluorescent analysis (Fig. 1). They were ≥3.0% in 10 subjects and ≤1.0% in 6. The upper limit of normal was regarded as 6.0%, which was the sum of the average and twice the standard deviation of the mean of the 24 subjects. The average

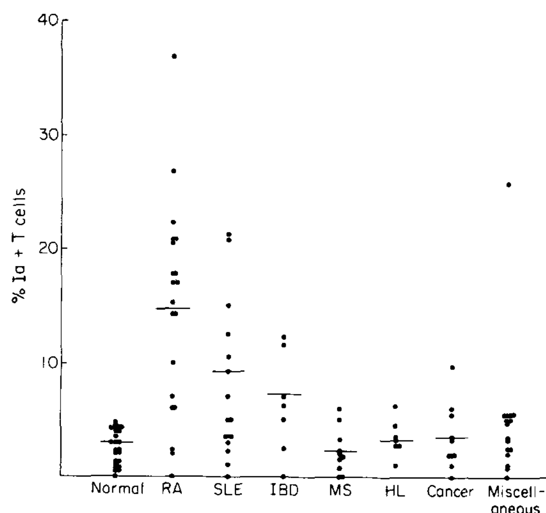

FIG. 1. Percentages of Ia^+ cells in the T preparations of normal individuals and patients with various conditions. RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; IBD, inflammatory bowel diseases; MS, multiple sclerosis; HL, hyperlipidemia.

was 2.6%. These results were obtained by using $F(ab')_2$ fragments of the rabbit anti-Ia antibodies in a direct fluorescence assay.

Somewhat higher values were obtained for the same anti-Ia rabbit antiserum by the sensitive rosette assay employing bovine RBC coated with isolated antibodies to rabbit Ig (Table I). For 10 normal individuals a range of 7.3–15.0% was obtained. As a control, normal rabbit serum was used in place of the anti-Ia antiserum, which was essential because this was an indirect assay and T cells with Fc receptors could interfere. In most instances low background levels with normal rabbit serum were obtained, but significant levels were sometimes observed.

RHEUMATOID ARTHRITIS. After encountering a high percentage of Ia^+ T cells in an initial patient with rheumatoid arthritis, a large population of rheumatoid arthritis patients was studied by fluorescence. In 21 of the 23 patients, the percentage of these cells exceeded the upper limit of the normal values (Fig. 1). In 14 of the 23 patients, the values exceeded 10%. As in those samples obtained from normal subjects, approximately one-half to three-fourths of the cells observed here and subsequently in patients with other diseases were stained rather faintly. 9 of the 23 patients were regarded by their physicians as having clinically active disease; the majority were not receiving corticosteroids or immunosuppressive therapy. The two patients with normal percentages of Ia^+ T cells were relatively inactive cases.

The elevated levels in the rheumatoid arthritis patients were also apparent using the rosette assay. Table I shows the results for nine patients as compared with the values obtained by fluorescence.

Fluorescence studies were also carried out with antibodies from a hybridoma that had been demonstrated to show Ia specificity very similar to the rabbit antiserum. The elevated levels in rheumatoid arthritis were clearly apparent with the hybridoma antibodies, and very parallel results to those illustrated for the rabbit antiserum were obtained (Table II).

TABLE I

Percentages of Positive T Cells from Normal Individuals and Patients with Rheumatoid Arthritis Determined by Fluorescence and by Rosette Assays Using the Heteroantiserum

	Positively stained cells	RFC
Normal subjects		
1	4.8	15.0 (2.0)*
2	3.0	11.7 (0.5)
3	2.4	12.3 (0.9)
4	2.4	8.0 (0.0)
5	2.0	12.4 (5.0)
6	2.0	11.3 (0.0)
7	2.0	7.3 (1.0)
8	1.2	7.7 (1.0)
9	0.8	13.7 (1.4)
10	0.5	9.0 (3.0)
Rheumatoid arthritis		
1	36.5	32.8 (0.0)
2	32.0	39.7 (2.5)
3	28.0	40.0 (3.0)
4	17.0	30.9 (2.0)
5	16.5	23.0 (0.0)
6	9.9	28.4 (2.4)
7	9.0	12.0 (0.0)
8	7.0	25.1 (ND)‡
9	3.2	7.6 (ND)

* Background levels with normal rabbit serum.
‡ Not done.

SYSTEMIC LUPUS ERYTHEMATOSUS. The Ia^+ T cells of 16 patients with systemic lupus erythematosus ranged from 1.4 to 21.2% by fluorescence analysis. In nine of them the percentages were above the normal values. In seven of them the values exceeded 10%. Most of the patients were receiving steroids when examined; the role of such therapy was not examined here.

MISCELLANEOUS DISEASES WITH ELEVATED LEVELS. Three patients with active bacterial infections had elevated levels of Ia^+ T cells by immunofluorescence. They suffered from staphylococcal aureus osteomyelitis, pneumococcal pneumonia, and acute cholecystitis. The percentages of Ia^+ T cells by fluorescence were 25.4, 13.9, and 18, respectively. One patient with idiopathic thrombocytopenic purpura had 25.7% Ia^+ T cells. Four of six patients with inflammatory bowel diseases also had mildly elevated percentages ranging from 6.3 to 12.3.

DISEASES WITHOUT ELEVATED LEVELS. Out of 10 patients with multiple sclerosis, 8 with hyperlipidemia, 3 with degenerative joint disease, and 10 with nonlymphomatous tumors of various organs not on chemotherapy, elevated levels were detected in only one patient with hyperlipidemia and one with salivary gland adenocarcinoma. The values in these two subjects were 6.3 and 9.8% by immunofluorescence, respectively. Patients with the following disorders had normal percentages of Ia^+ T cells: recent operation for abdominal aneurysm, chronic obstructive lung disease, acute thrombophlebitis of lower extremity, recent myocardial infarction, chronic rheumatic disease,

TABLE II
Percentages of T Cells Stained by the Rabbit Anti-Ia Antiserum and by the Monoclonal Antibody

	Rabbit anti-Ia	Monoclonal antibody
Normal subjects		
1	4.8	5.0
2	3.0	2.5
3	2.5	1.5
4	1.0	0.0
5	0.5	1.0
Rheumatoid arthritis		
1	11.0	10.0
2	22.5	17.5
3	12.5	10.0
4	15.2	16.3

pulmonary embolism, alcoholic gastritis with bleeding, asthma, diabetes mellitus, alcoholic gastritis with megaloblastic anemia, cerebrovascular accident, and subacute sclerosing penencephalitis.

SEROTYPES OF B AND T CELLS. The allospecificity of the Ia antigens on the B cells of three rheumatoid arthritis patients was determined by the microcytoxicity technique (14). Their T lymphocytes were stained with alloantisera of predetermined specificity as described. Considerable background staining was obtained with normal serum and all the alloantisera, probably a reflection of the Fc receptors on the T lymphocytes. However, in each individual, the highest values were obtained by the antisera that also reacted with the individual's B lymphocytes. Similar studies were carried out in normal individuals. The percentages of positively stained cells were much less (Table III).

Immunization Effects

In view of the known in vitro effects of mitogens and MLC reactions on the generation of Ia^+ T cells, the in vivo effects of immunization were studied that might be relevant to the increased numbers of Ia^+ T cells in disease. Normal subjects who had received tetanus immunization 5–10 yr previously were given an injection of tetanus toxoid. Elevated levels of Ia^+ T cells were produced and this occurred within 2 d after the injection. Fig. 2 illustrates the results in one individual utilizing the rabbit antiserum. Also shown is the curve for Ia^+ T cells after in vitro stimulation with tetanus toxoid for the same individual. The markedly slower onset of positive T cells in the in vitro response is apparent. Similar results were obtained in three other individuals. The character of the positive cells also differed very significantly in the in vitro and the in vivo response. The cells in the latter cases were small T cells whereas in the in vitro case large blastoid cells were involved.

Similar results were obtained after purified protein derivative (PPD) administration (Fig. 3). Again a rapid rise was observed after in vivo stimulation, and the cells involved were very similar to those observed for the tetanus system. Also plotted in this case is the curve utilizing the anti-DRw3 alloantiserum. This appropriate specificity, known from B-cell typing on this individual, follows the curve obtained

TABLE III

Percentages of T Cells from Rheumatoid Arthritis Patients and Normal Subjects Stained by Anti-DR Alloantisera in Indirect Fluorescence Assay Compared with Heteroantiserum Staining by Direct Fluorescence

B-Cell types	Rheumatoid arthritis			Normal	
	C.R.	J.V.	C.S.	R.W.	J.P.
	(DRw4)*	(DRw4)*	(DRw3,4)*	(DRw3,4)*	(DRw2,4)*
Rabbit anti-Ia	23	23	19.5	1.6	0.6
Normal human serum	5	6	9	2.5	0.8
Serum 191 (anti-DRw4)	17	19	29	0.8	1.3
Serum 932 (anti-DRw3)	5	5	27	3.4	1.3
Serum 2359 (anti-DRw7)	8	2	6	1.5	1.2

* Phenotype as determined by microcytotoxicity assay on purified B cells.

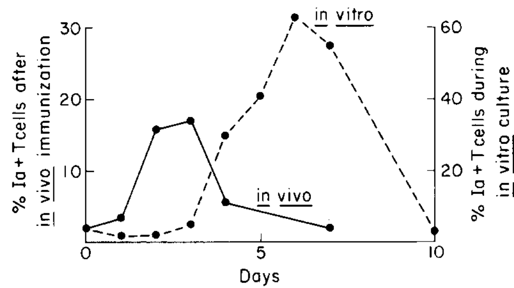

FIG. 2. Effect of in vivo immunization and in vitro culture with tetanus toxoid on the percentages of Ia^+ T cells.

with the rabbit Ia antiserum. The inappropriate specificity control showed negative results.

Miscellaneous Studies

Cytocentrifuge preparations of the peripheral blood T lymphocytes were made from three rheumatoid arthritis patients whose Ia^+ cells were 20.0, 20.8, and 5.9%. Less than 0.2% of the cells appeared morphologically as lymphoblasts. Similar preparations were also examined for the T cells of one of the subjects who received the PPD. The percentages of lymphoblasts remained $<2\%$ at a time when the Ia^+ cells were 25%.

T-lymphocyte preparations from four rheumatoid arthritis patients whose Ia^+ T cells were 5.9, 14.4, 17.8, and 20.8% were examined by autoradiography. Less than 0.1% of the cells from each case incorporated radioactive thymidine.

Studies were also carried out in normal and rheumatoid arthritis patients on whether the Ia^+ cells were in the T_γ or non-T_γ fraction of T cells. Isolation of the T_γ fraction showed definite enrichment of Ia^+ cells, which, in some instances, were as high as 50% of the T_γ cells. However, in both the normals and the rheumatoid arthritis patients, significant numbers of Ia^+ cells were found in the non-T_γ fraction, which was virtually free of contaminating T_γ cells. In addition, certain of the patients showed levels of Ia positive T cells that were considerably higher than the T_γ levels. These relationships were clearly complex and will be published in detail separately.

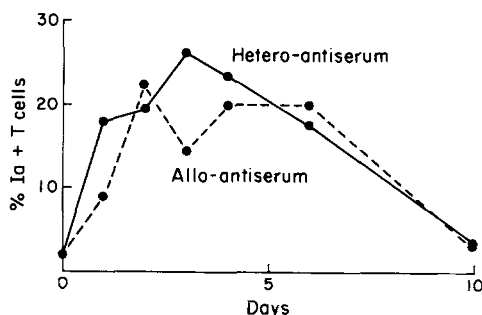

Fig. 3. Effect of in vivo skin test with PPD on the percentages of T cells stained by rabbit anti-Ia antiserum and anti-DRw3 alloantiserum.

Discussion

It is apparent from our study that increased numbers of Ia^+ T cells frequently appear in the circulation in disease. This was especially striking in patients with rheumatoid arthritis and systemic lupus erythematosus, but also evident in patients with infections and a number of miscellaneous conditions. Various metabolic disorders showed close to normal levels. It is of special interest that patients with multiple sclerosis also showed normal levels, in striking contrast to patients with systemic lupus erythematosus and rheumatoid arthritis, diseases with multiple autoimmune manifestations. Although well over 100 individuals were examined in our survey, the study remains incomplete and other specific disorders require investigation. A limited earlier survey from our laboratory did not reveal elevated levels in patients with immune deficiency disease; however, one patient with elevated levels has been reported (15). In addition, patients with infectious mononucleosis and graft-vs.-host disease have been found to have high levels (9, 10).

In a previous study (5), it was demonstrated that a small but definite number of Ia^+ T cells is found in normal individuals. This was confirmed in this study, and a mean of 2.6% was found, a value very similar to that reported recently by another group of investigators (16). Our study demonstrated that blast cells were not significantly involved and the Ia^+ normal and disease T cells were very similar and consisted primarily of small lymphocytes. They clearly differed from the in vitro stimulated Ia^+ T cells, which are almost entirely large blastoid cells. The studies in diseases where these cells reached very substantial levels add significance to the cells found in normal individuals despite their low concentration.

To corroborate that the increases in the positively stained cells were indeed Ia^+, two other types of antisera were used in addition to the highly specific rabbit antiserum primarily employed and previously described (4, 5), a broadly reactive anti-Ia hybridoma and alloantisera of known DR specificity. The results obtained with the monoclonal antibodies were very similar to those obtained by the rabbit anti-Ia antiserum. The results with the alloantisera indicated that the allospecificities of the Ia^+ T cells were the same as those of the B lymphocytes from the same individual. Besides using the immunofluorescent reagents, Ia^+ cells were also detected by the indirect rosette technique (17). This was carried out by first sensitizing the lymphocytes with rabbit anti-Ia antiserum and then rosetting them with bovine RBC to which were coupled isolated sheep anti-rabbit-Ig antibodies. The percentages of

RFC were somewhat higher than the immunofluorescent positive cells in line with the known greater sensitivity of this rosette method.

The chief clue regarding the significance of the Ia^+ T cells described above was gained from a study of the effects of immunization of normal individuals. Administration of tetanus toxoid or PPD in sensitized subjects who developed reactions at the site of injection resulted in a marked increase in the number of circulating Ia^+ T cells. An increase from an initial level of 1.6 to 28% was observed in one instance. These Ia^+ T cells closely resembled those observed in the normal and diseased individuals, and, again, blastoid cells were not significantly involved. It is of special interest that the positive T cells appeared quite soon after immunization, usually within 48 h. This stood in marked contrast to the late appearance of Ia^+ T blasts after in vitro stimulation with the same antigens and the cells of the same individuals.

The exact origin and significance of these Ia^+ T cells remains to be elucidated. Their enrichment in the T_γ fraction of T cells indicates that they are present in this fraction. However, they clearly also were present in the non-T_γ fraction. Thus it would appear that more than one T-cell fraction is involved, although it is not as yet clear how selective a fraction the T_γ really is. The similarity between the situation in the normal and the elevations in disease suggests that these cells might be recruited into the circulation after antigen injection in sensitized individuals or during disease processes involving antigenic stimulation. Another possibility is that they result from some type of stimulation by antigens. Numerous workers have described small numbers of blastoid cells and DNA-synthesizing cells in the circulation of individuals with some of the diseases described above (18–22). Our studies indicate that such cells do not account for the Ia^+ T cells observed; however, the Ia antigens might have developed from minor degrees of T-cell stimulation without overt blastogenesis or cell division, although such cells were not observed during in vitro stimulation. It also remains a possibility that the Ia antigens are derived from other cells such as stimulated B cells or macrophages and are simply adsorbed to the surface of the T cells. Evidence against this was obtained from elution studies where these antigens failed to be removed under conditions known to cause elution of some adsorbed Ia antigens. In addition, serial determinations in normal individuals and patients with rheumatoid arthritis showed a relative constancy of the positive T-cell levels. Irrespective of the precise mechanism involved in the development of these cells, their wide occurrence in patients with rheumatoid arthritis, a disease of unknown etiology, appears of special interest and may furnish new guides for further work in this disease.

Summary

The Ia antigens, usually expressed primarily on B lymphocytes, are found on a small percentage of normal peripheral blood T cells (average 2.6% by fluorescence and 10.8% by rosette assay). Elevated levels up to 40% by both assays were observed in a high proportion of patients with rheumatoid arthritis. Increases also were found in patients with systemic lupus erythematosus and various types of infections. The increases were evident with a specific heteroantiserum, a hybridoma reagent, and DR specific alloantisera. Normal levels were present in multiple sclerosis and an assortment of metabolic and other disorders. A rise in similarly positive T cells occurred in normal individuals after immunization with tetanus toxoid or PPD. The cells primarily involved in all of these instances were small lymphocytes, which stained

relatively weakly with the fluorescent reagents and were readily distinguishable from T-cell blasts. They were found to be enriched in isolated T_γ fractions but were also found in other T cells. The accumulated evidence indicated that these cells represent an expansion of one or more subsets of T cells found in normal individuals, and that their level in the peripheral blood may serve as an index of immunological stimulation.

Received for publication 18 September 1979.

References

1. Winchester, R. J., S. M. Fu, P. Wernet, H. G. Kunkel, B. Dupont, and C. Jersild. 1975. Recognition by pregnancy serums of non-HL-A allo-antigens selectively expressed on B lymphocytes. *J. Exp. Med.* **141**:924.
2. Mann, D. L., L. Abelson, S. Harris, and D. B. Amos. 1975. Detection of antigens for B-lymphoid cultured cell lines with human allo-antisera. *J. Exp. Med.* **142**:84.
3. Cresswell, P., and S. S. Geier. 1975. Antisera to human B-lymphocyte membrane glycoproteins block stimulation in mixed lymphocyte culture. *Nature (Lond.).* **257**:147.
4. Winchester, R. J., C. Y. Wang, J. Halper, and T. Hoffman. 1976. Studies with B cell allo- and heteroantisera: parallel reactivity and special properties. *Scand. J. Immunol.* **5**:795.
5. Fu, S. M., N. Chiorazzi, C. Y. Wang, G. Montazeri, H. G. Kunkel, H. S. Ko, and A. B. Gottlieb. 1978. Ia-bearing T lymphocytes in man. Their identification and role in the generation of allogeneic helper activity. *J. Exp. Med.* **148**:1423.
6. Ko, H. S., S. M. Fu, R. J. Winchester, D. T. Y. Yu, and H. G. Kunkel. 1979. Ia determinants on stimulated human T cells. *J. Exp. Med.* **150**:246.
7. DeWolf, W. C., S. F. Schlossman, and E. J. Yunis. 1979. DRw antisera react with activated T cells. *J. Immunol.* **122**:1780.
8. Evans, R. L., T. J. Faldetta, R. E. Humphreys, D. M. Pratt, E. J. Yunis, and S. F. Schlossman. 1978. Peripheral human T cells sensitized in mixed leukocyte culture synthesize and express Ia-like antigens. *J. Exp. Med.* **148**:1440.
9. Johnsen, H. E., M. Madsen, T. Kristensen, and F. Kissmeyer-Nielsen. 1978. Expression of HLA-DR determinants on human T cells in infectious mononucleosis. *Scand. J. Immunol.* **8**: 160. (Abstr.)
10. Reinherz, E. L., R. Parkman, J. Rappeport, F. C. Rosen, and S. F. Schlossman. 1979. Aberrations of suppressor T cells in human graft-versus-host disease. *N. Engl. J. Med.* **300**: 1062.
11. Lemke, H., G. J. Hammerling, C. Hoffman, and K. Rajewsky. 1978. Hybrid cell lines secreting monoclonal antibody specific for major histocompatibility antigens of the mouse. *Nature (Lond.).* **271**:249.
12. Wang, C. Y., S. M. Fu, and H. G. Kunkel. 1979. Isolation and immunological characterization of a major surface glycoprotein (gp54) preferentially expressed on certain human B cells. *J. Exp. Med.* **149**:1424.
13. Gottlieb, A. B., S. M. Fu, D. T. Y. Yu, C. Y. Wang, J. Halper, and H. G. Kunkel. 1979. The nature of the stimulatory cells in human allogeneic and autologous MLC reaction. *J. Immunol.* **123**:1497.
14. Gibofsky, A., R. J. Winchester, M. Patarroyo, M. Fotino, and H. G. Kunkel. 1978. Disease associations of the Ia-like human alloantigens. Contrasting patterns in rheumatoid arthritis and systemic lupus erythematosus. *J. Exp. Med.* **148**:1728.
15. Reinherz, E. L., A. J. Strelkauskas, A. Rubinstein, S. F. Schlossman, and F. S. Rosen. 1979. Functional and phenotypic characterization of a suppressor T cell in acquired agammaglobulinemia. *Clin. Res.* **27**:474. (Abstr.)
16. Greaves, M. F., W. Verbi, H. Festenstein, C. Papasteriadis, D. Jaragnemada, and A. Hayward. 1979. "Ia-like" antisera on human T cells. *Eur. J. Immunol.* **9**:356.

17. Sandrin, M. S., H. A. Vaughan, I. F. C. Mckenzie, B. D. Tait, and C. R. Parish. 1979. The human Ia system: definition and characterization by xenogeneic antisera. *Immunogenetics.* **8:** 185.
18. Bond, V. P., E. P. Cronkite, T. M. Fliedner, and D. K. Schorke. 1958. Desoxyribunucleic acid synthesizing cells in peripheral blood of normal human being. *Science (Wash. D. C.).* **128:**202.
19. Bacon, P. A., R. L. Sewell, and D. Crowther. 1975. Reactive lymphoid cells ("immunoblasts") in autoimmune and haematological disorders. *Clin. Exp. Immunol.* **19:**201.
20. Crowther, D., G. Hamilton Fairley, and R. L. Sewell. 1969. Lymphoid cellular responses in the blood after immunization in man. *J. Exp. Med.* **129:**849.
21. Rubini, J. R., V. P. Bond, S. Keller, T. M. Fliedner, and E. P. Cronkite. 1961. DNA synthesis in circulating blood leukocytes labeled in vitro with ^{3}H-thymidine. *J. Lab. Clin. Med.* **58:**751.
22. Gump, D. W., and Fekety. 1967. The relationship of infection and DNA synthesizing cells in human blood. *J. Lab. Clin. Med.* **69:**428.