Henry Ford Hospital Medical Journal

Volume 27
Number 3 *John W. Rebuck Testimonial Issue*

Article 6

9-1979

Lymphocytes: 1979

Sudhir Gupta

Robert A. Good

Follow this and additional works at: https://scholarlycommons.henryford.com/hfhmedjournal

Part of the Life Sciences Commons, Medical Specialties Commons, and the Public Health Commons

Recommended Citation
Gupta, Sudhir and Good, Robert A. (1979) "Lymphocytes: 1979," *Henry Ford Hospital Medical Journal* : Vol. 27 : No. 3 , 224-235.
Available at: https://scholarlycommons.henryford.com/hfhmedjournal/vol27/iss3/6

This Article is brought to you for free and open access by Henry Ford Health System Scholarly Commons. It has been accepted for inclusion in Henry Ford Hospital Medical Journal by an authorized editor of Henry Ford Health System Scholarly Commons.

Henry Ford Hosp Med Journal
Vol 27, No 3, 1979

Lymphocytes: 1979†

Sudhir Gupta, MD* and Robert A. Good, PhD, MD**

Rapid progress has been made in understanding the complexity of the immune system. The current status of lymphocyte subpopulations with regard to ontogenic development, their surface and intracellular markers, and functions in various immunologic phenomena has been reviewed. Heterogeneity of T lymphocytes as defined by receptors for immunoglobulin isotypes is discussed in detail. Various cell types and their products involved in immunoregulation are also presented.

Lymphocytes play a critical role in immune responses. During the last twenty years rapid progress has been made in immunobiology to clarify the role of lymphocytes in immunological phenomena in animals and man. Studies in experimental animals and in experiments of nature in humans led to the discovery of two major lymphoid components of specific immunity (Fig. 1). Both lines of lymphoid cells derive from a common, primitive precursor stem cell. Committed lymphoid stem cells follow different routes of differentiation and maturation into T and B lymphocytes. By one route, they enter the thymus and under its inductive influences begin a sequence of differentiation stages to mature into immunoregulatory and effector T cells that perform functions of cell-mediated immunity. By an alternate route, stem cells are processed in fetal liver and later in bone marrow. These differentiate and mature into B cells, which on terminal differentiation become plasma cells highly specialized to synthesize and secrete specific antibody. These cells thus subserve the function of humoral or antibody-mediated immunity. During differentiation and maturation, lymphocytes develop surface receptors and differentiation antigens and many distinct functions. The studies of cell surface receptors and the development of methods for identifying and separating the several subpopulations have contributed greatly to understanding the lymphoid system and its functions as effector cells and as regulators and monitors of the immunologic adaptations.

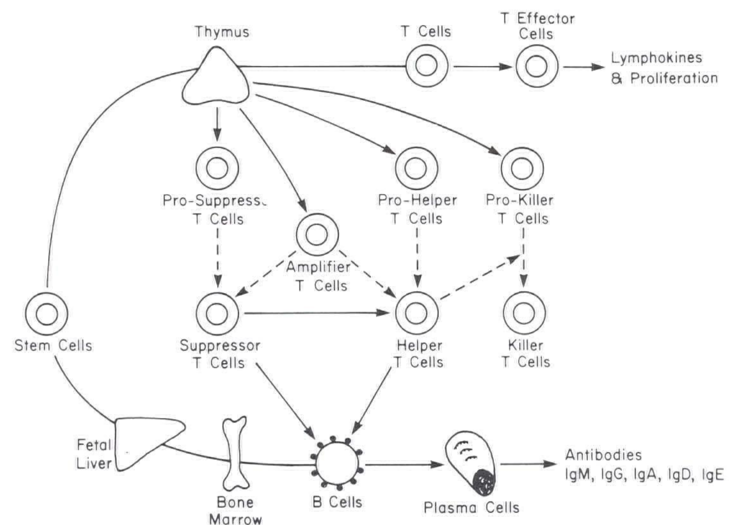

Fig. 1

Ontogeny of T cell lineage

The thymus originates at about six weeks of gestation from the junction of the ectodermal and endodermal epithelium of the third and fourth pharyngeal pouches as a single layer of epithelial cells. In man, lymphocytes are demonstrable within this organ by the eighth and ninth week of gestation. The epithelial anlagen of the thymus appears at about the

† The original work cited in this article was aided by grants from the National Institutes of Health CA-17404, CA-19267, CA-08748, CA-23766, AI-11843, NS-11457, AG-00541, and from the Fund for the Advanced Study of Cancer.

* Associate Member, Sloan-Kettering Institute for Cancer Research, New York

** President and Director, Sloan-Kettering Institute for Cancer Research, New York
Address reprint requests to Dr. Gupta, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10021

10th embryonal day and has been invaded by mesenchymal cells by the 11th or 12th day. Animal studies indicate that precursors of lymphoid cells appear in the fetal liver and migrate to the thymic epithelium (1). In man at the 11-19th week of gestational age, thymus contains up to 65% cells that form rosettes with sheep RBC (SRBC) (2).* Stites and associates (3) reported that almost all fetal thymocytes between 12-20 weeks of gestation react specifically with antifetal thymocyte serum, as demonstrated by indirect immunofluorescence technique. Antigen-binding cells are maximal in fetal thymus and represent a smaller population in the thymuses of children and young adults (4).

The proliferative response of fetal thymocytes to PHA (5) begins as early as the 14th week of gestation and increases until the 18th week, after which responses decline to adult levels (6). The appearance of proliferative responses of thymocytes to PHA correlates with the demarcation of thymus into cortex and medulla (7). Further morphological study suggests that thymic medulla contains these PHA-responsive thymocytes (6). PHA-responsive lymphocytes appear in the spleen two weeks after such cells appear in the thymus (8), but bone marrow and fetal liver cells fail to respond to PHA at this time (9).

The ontogeny of responding cells in one-way, mixed leukocyte culture reaction (MLR) has been studied by a number of investigators. Stites, et al (9) have reported the presence of MLR-responsive cells in fetal liver as early as 7.5 weeks of gestational age. Carr and associates (10) demonstrated no clear correlation between a strong response of lymphoid cells from fetal liver to allogeneic cells and failure to respond to PHA. MLR-responsive cells were also present in fetal spleen and thymus. These observations suggest that capacity for MLR may be distinct and more primitive than reactivity to PHA. PHA-induced, cell-mediated cytotoxicity is lacking from fetal thymuses (14-18 weeks gestational age) at a time when fetal bone marrow cells respond to PHA by developing cytotoxic potential against target chicken RBC. By contrast, at the same developmental stage these cells failed to proliferate in response to PHA (11). Peripheral blood and splenic lymphocytes from the same fetuses proliferated and became cytotoxic in response to PHA, while liver lymphoid cells failed to respond in either test.

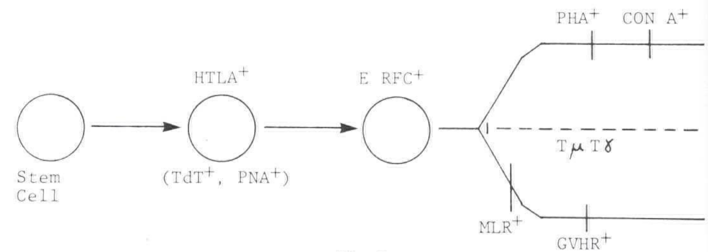

Fig. 2

The fetal lymphoid cells capable of producing graft versus host reaction (GVHR) are present in splenocytes from 13-23 week-old fetuses. No definitive information is available as to the earliest appearance of cells capable of influencing GVHR (12).

Touraine, et al (13,14) studied *in vitro* and *in vivo* expression of differentiation markers on cells of T cell lineage by incubating the bone marrow cells with thymic factors *in vitro* and by sequential study of patients with DiGeorge syndrome who had received thymic transplants. The scheme derived from these studies indicates a sequential and bifurcated development of T cells (Fig. 2). Hirano, et al (14a) have brought forward evidence to support this interpretation which uses definition of T lymphocyte subpopulations by antisera against T cell lines.

Receptors for peanut agglutinin and high terminal deoxynucleotidyl transferase (TdT) activity appear to be very early markers for identifying cells in the T cell lineage. However, these two receptors do not appear to be confined exclusively to cells of T cell lineage. The binding sites of peanut agglutinin, for example, are present on cells from Burkitt lymphoma (B cell lineage) and from acute myeloid leukemia (15). Similarly, high TdT activity has been reported in the malignant cells of patients with pre-B cell leukemia (16). Therefore, it is evident that these two markers are features of relatively immature cells of both lymphoid and nonlymphoid lineage. Among cells of the T cell lineage, they are present on pre-T or relatively immature T cells but are lacking from mature T cells. Our studies of T cell subsets obtained from various lymphoid organs, as identified by receptors for Ig, demonstrated that SRBC rosette-forming

*__Abbreviations used in this paper:__
ADCC — antibody-dependent cellular cytotoxicity
Con A — Concanavalin A
EBV — Epstein-Barr virus
ERFC — sheep RBC rosette forming cells
GVHR — graft-versus-host reaction
HTLA — human T lymphocyte antigen
MIF — migration inhibition factor
MLR — mixed leukocyte culture reaction
MHC — major histocompatibility complex
MRBC — mouse red blood cells
nk — natural killer
PNA — peanut agglutinin
PHA — phytohemagglutinin
PWM — pokeweed mitogen
SRBC — sheep red blood cells
TdT — terminal deoxynucleotidyl transferase
Tμ — T cells with receptors for IgM
Tγ — T cells with receptors for IgG
Tα — T cells with receptors for IgA

thymocytes lack receptors for IgM (Tμ), IgG (Tγ), or IgA (Tα) receptors. These findings suggest that Ig receptors on T cells develop after receptors for SRBC have appeared (17-19).

Ontogeny of B cell lineage

The ontogeny of mammalian B cells has been most extensively studied in mice. The earliest identifiable cell is a large cell with intracytoplasmic IgM but without surface IgM that appears in the liver of 12-13 day-old mouse fetus (20-22). B cells with surface IgM first appear in the fetal liver around 16-17 days of gestation; they have now also been found in rabbits and human fetal liver and in the bursa of Fabricius of the chick embryo (23,24). In man, pre-B cells were present in the fetal liver of a 5-7 week fetus which lacked any surface IgM + B lymphocytes (24).

According to morphologic and kinetic studies, pre-B cells appear divisible into two classes. Large pre-B cells (17 μ) have a deeply indented or convoluted nucleus and represent a rapidly dividing cell population. Small pre-B cells (8 μ) are morphologically similar to surface IgM + B cells but lack surface IgM and divide slowly. In the human, mouse, and rabbit, pre-B cells are found predominantly in the fetal liver and bone marrow but may be present in lower frequencies in fetal spleen and lymph nodes. The study of pre-B cell leukemias (16) demonstrated that Ia antigen was present on pre-B cells. Up to the 13th week of gestation, they outnumber surface IgM + B cells in fetal liver. B lymphocytes bearing only surface IgM develop earlier than do cells bearing other Ig classes (25,26), e.g., those that express surface IgD, IgG or IgA. Initially, IgD appears exclusively on immature B cells which also bear surface IgM. The ratio of lymphocytes with surface IgM alone to those bearing both IgM and IgD probably serves as a good index of maturity of a B cell population. The position in the sequence of appearance of lymphocytes with surface IgE in human fetuses has not yet been elucidated (Fig. 3). However, a study of hooded Lister strain rats (27) demonstrates that surface, IgE-bearing B lymphocytes are derived from B cells with surface IgM. Observations in rat, mouse, and now in human, concur with the view that precursors for each immunoglobulin class of B cells are derived directly from separate surface IgM-bearing cell lines (Fig. 3). While Fc receptor-positive lymphoid cells are found in human fetal liver as frequently as surface IgM + B cells (26), large pre-B cells do not bear Fc receptors. Complement receptor (C_3) bearing lymphoid cells are present in fetal liver in proportions much smaller than those for cells with surface IgM and / or Fc receptors and are lacking in the early gestational period when the other two receptors are present. The receptor for mouse RBC (MRBC) is present as early as surface IgM and perhaps is present on pre-B cells. A scheme of sequential development of receptors on cells of B cell lineage is shown in Fig. 4.

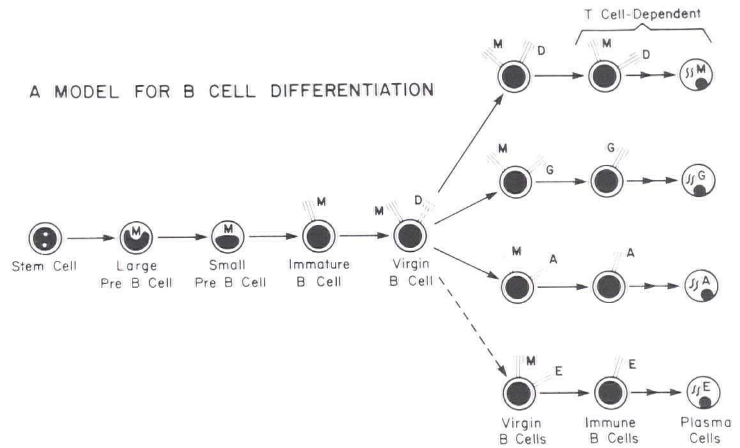

Fig. 3

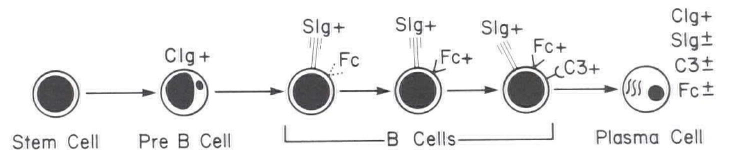

Fig. 4

Markers of human lymphoid cells

During differentiation and maturation, lymphoid cells display a variety of cell surface markers. Based on surface marker analysis, they have been classified into three major subpopulations: T, B, and so-called third population or null cells (Table I).

Lineage of B lymphocytes

Pre-B lymphocytes of mouse and man are characterized by the presence of intracytoplasmic IgM without surface IgM. They are present in very small numbers (~1%) in the bone marrow of young adults but are absent from the peripheral blood. Malignant proliferations of the pre-B cell population have now been reported (16). Although indirect evidence suggests that receptors for MRBC are present on pre-B cells, direct evidence is lacking. Receptors for MRBC are also present on a subset of mature B cells (28-30). Studies of ontogeny as well as of blood from patients with lymphoproliferative disorders suggest that MRBC receptors appear on B cells at an early stage of maturation but not on B cells and plasma cells that actively secret Ig.

B lymphocytes are identified by the presence of surface Ig that is the product of the cell carrying Ig on its surface. Approximately 10^5 receptor Ig molecules are present on a single B cell and approximately 10-14% of peripheral blood lymphocytes express such surface Ig. Surface IgM-bearing lymphocytes comprise most of the circulating B lymphocytes, whereas only a minor population of B lymphocytes in the circulating blood have surface IgG, IgA, or IgE. Among IgG subclasses, IgG_2 appears to be dominant on the surface

TABLE I
Markers of Human Lymphoid Cell Subpopulations

B Cell Lineage	
Stem Cell	?Alloantigen
Pre-B Cells	Intracytoplasmic IgM ?MRBC receptors "Ia like" antigen
B Cells	Surface immunoglobin MRBC receptors Epstein-Barr Virus receptor IgG Fc receptors IgM Fc receptors IgA Fc receptors Complement component receptors B cell alloantigens ("Ia like")
T Cell Lineage	
Stem Cell	?Alloantigen
Pre-T Cells	Terminal deoxynucleotidyl transferase (TdT) HTLA Peanut agglutinin
T Cells	HTLA SRBC receptors Acid α-naphthyl acetic esterase IgG Fc receptors ($T\gamma$) IgM Fc receptors ($T\mu$) IgA Fc receptors ($T\alpha$) T_{H2} antigen Histamine receptors
Third Population "Unclassified" Lymphoid Cells	IgG Fc receptors Complement component receptors Receptors for EBV "Ia like" antigen

of B lymphocytes (33). A restriction to Ig class or IgG subclass and to Gm antigens has been demonstrated on lymphocyte membrane (33). However, both IgM and IgD can be regularly demonstrated on the same cell (34,35). Using idiotypic antisera, it has been shown that IgD and IgM on the same cell have identical hypervariable regions and therefore appear to employ the same gene to code for their variable regions of the Ig (35). IgD is the most susceptible to proteolysis, but its precise role still remains to be defined. Bourgois and associates (36) have suggested that it may play a regulatory role by eliciting an anti-idiotypic response. Immature B cells possess surface IgM only; mature B cells possess both IgM and IgD. Following activation by antigen or mitogen, IgD is lost. Because immature B cells are very susceptible to tolerance induction, we suggest that IgD prevents tolerance induction and facilitates the positive immunological adaptation.

Receptors for IgG Fc are present on cells from all hematopoietic cell lineages. They are also present on B cells, on lymphoid cells of the "third" population, and on a subpopulation of T cells. Fc receptors on B cells and on third population cells can be distinguished from each other (37) because the former have a lower affinity for complexed IgG than the latter. The concentration of soluble immune complexes required to detect binding to the Fc receptors of third population cells is 100 times fewer than that required to detect B cell Fc receptors. Third population cells are active in antibody-dependent (ADCC) and natural cytotoxicity (nk), whereas B cells do not mediate such cytotoxicities (38). Fc receptors on B lymphocytes have a close spatial association with "Ia like" antigens; however, no such association has been reported on the surface of cells of the third population. B cell Fc receptors via this association may play a significant role in the regulation of immune response.

In recent years, an interrelationship between components of the complement system and cells of the immune system has been recognized. B lymphocytes express membrane receptors for C_3b, C_3d, C_4b, C_1q, C_8, and C_2 inhibitor (39-42). Factor B activity is associated with peripheral B cells, cells from chronic lymphocytic leukemia (CLL), and Raji cells of Burkitt's lymphoma. Factor B is present intracellularly and not on the surface of B cells. Thymocytes and erythrocytes lack factor B activity. Since lymphocyte factor B is distinct from C_3b receptor, serum factor B cannot be regarded as fluid phase receptor for C_3b. Receptors for C_3 are trypsin sensitive and are present on most but not all B lymphocytes. Approximately 6000 C_3 molecules are required for maximal binding to a lymphocyte. C_3b and C_3d receptors, which appear to be serologically distinct from each other, cap independently on the lymphocyte surface. The C_4b receptor is present on all of the same cell types which have C_3d receptors, except for a few lymphoblastoid lines with receptors for C_3b only (41,42). The biological function of the C_4b and C_3 receptors appears similar. Receptors for C_1q are present on both T and B lymphocytes. This receptor is sensitive to treatment with trypsin but resists treatment with neuraminidase or DNase. Although the biological significance of C_1q receptors is not known at present, it has been proposed that they bind to immune complexes, and this binding activates a complement sequence that in turn can result in change of cellular activity. C_3 receptors appear to play a part in induction of thymus-dependent antibody production. Complement receptors may participate in the initial events taking place on the lymphocyte surface during antigenic stimulation that leads to antibody production. They may also contribute to the follicular localization of antigen (45) and the antibody-dependent mechanism that brings antigenic substances to certain areas in lymphoid organs, presumably for the induction of immune response (46,47).

Epstein-Barr Virus (EBV) is a lymphotropic virus for man and for New World monkeys. Jondal and Klein (48) demonstrated the presence of EBV receptor on some B cells of long-term, culture-maintained lymphoid cell lines, although it is lacking from T cells. Greaves, et al (49) also reported that EBC receptors are present on virtually all B cells but not on T cells and thymocytes.

In addition to the classical, serologically defined antigens of the major histocompatibility system (HLA-A, B, C), the HLA-gene complex also includes determinants which regulate the ability of cells to stimulate in MLC. In man, during studies of certain alloantisera that selectively inhibited MLC, antibodies were present which exhibited a striking specificity for alloantigens present on B cells but not on T lymphocytes (50). These antigens are distinct from HLA determinants and are designated as HL-B or "Ia like" antigens. At least two genetic loci in MHC appear to be responsible for the synthesis of these polymorphic allotypic antigens. It has now become clear that "Ia like" antigens are not restricted to B lymphocytes but are also present on monocytes, precursors of granulocytes, and even on erythrocytes (51,52), sperm cells, Langerhan cells of skin, and a subpopulation of T cells (53), as well as the third population of lymphoid cells.

Lineage of T lymphocytes

It is likely that stem cells that have been committed to differentiate along the T cell lineage bear a definitive alloantigen, although this antigen remains to be defined. As discussed in the section of ontogeny of T cells, pre-T cells, relatively immature T cells and thymocytes have receptors for peanut agglutinin and possess high activity of TdT. Another antigen, the human T lymphocyte antigen (HTLA), is present on human thymocytes and also on both relatively immature and fully mature T cells (13,54). Receptors for SRBC are present on thymocytes and peripheral blood T cells and absent from other cells of hematopoietic lineage. The formation of rosettes between T lymphocytes and SRBC is very susceptible to technical variations which influence both the proportions of rosette-forming cells and the strength of SRBC binding to lymphocyte. While the biochemical nature of the receptor on T lymphocytes for SRBC is poorly understood, it is probably a glycoprotein synthesized within hours after enzymatic removal from the T lymphocytes by a process requiring protein synthesis but not cell replication.

Human peripheral blood T cells have receptors for Helix Promatia A hemagglutinin (HP), but it is also present on a subpopulation of B lymphocytes (55,56). There is evidence to suggest that the HP receptor on the B cells is also present on relatively immature cells (57).

Alpha-naphthyl acetate esterase (ANAE) activity has been used as an enzymatic marker to identify monocytes, but it can also be demonstrated in most T cells (58,59). However, the staining pattern is quite distinct from that seen on monocytes. Whereas ANAE-stained T cells reveal a discrete spotted pattern, monocytes reveal a homogeneous rim pattern. Knowles, et al (60) reported comparable proportions of ANAE positive and SRBC binding cells in the peripheral blood. However, discrepancies between these two markers were observed in thymus and spleen, where less ANAE activity was recorded in thymocytes than in SRBC rosette forming cells. Further, in the spleen ANAE activity was demonstrated in non-T cell fractions.

Human T lymphocytes demonstrate an extraordinary degree of heterogeneity, as evidenced by the presence of differentiating antigens (TH1 and TH2) as well as by receptors for immunoglobulins that exist on relatively distinct subsets of human T lymphocytes (61-69). TH1 and TH2 phenotypes have been defined either by heterologous anti-T cell antisera which have been absorbed on autologous B cell lines (for TH1) or by absorption with leukemic cells from a patient with T cell type CLL (for TH2). TH1+ cells respond by proliferation to mitogens, PHA, Con A, and allogeneic cells and produce migration inhibition factor (MIF). TH1+ cells do not respond by proliferation to soluble antigen but have allogeneic killer activity. TH2+ cells also respond poorly by proliferation to soluble antigens. This population appears to mediate a powerful killer activity in cell-mediated lymphocytes. Hirano, et al (14a) have identified surface antigen on human suppressor T cells by using an antiserum against human T leukemic cell line HSB absorbed with homologous B cell line. While this antiserum also identifies a population of T cells that respond in MLC, it has no effect on helper T cells or mitogenic response to PHA and Con A.

Recently, Strelkauskas, et al (70,71) have demonstrated that sera from patients with juvenile rheumatoid arthritis (JRA) contain antibodies that are directed against a subset of T lymphocytes. JRA + T cells proliferate in response to Con A but not to PHA and when isolated from normal individuals inhibit immunoglobulin biosynthesis of B cells in plaque forming cell (PFC) assay. In contrast, JRA negative T cells enhanced immunoglobulin production by B cells. These studies clearly demonstrate the presence of antisuppressor T cell antibodies in the sera of patients with JRA. It is evident that the serum from patients with autoimmune disease may provide readily available reagents for further dissection of functionally distinct subpopulations of human T cells.

Human T lymphocytes have also been shown to possess receptors for IgM ($T\mu$), IgG ($T\gamma$), or IgA ($T\alpha$) (63-69) which can be identified and enumerated by rosette-technique using OxRBC-IgM, IgG, or OxRBC-TNP-IgA complexes. The receptor for IgM on $T\mu$ cells has specificity for the Fc portion of the IgM molecule and appears to bind to the T cell receptors by its CH_4 domain (72). Both pentameric and monomeric IgM could bind to IgM receptors on $T\mu$ cells (73). It is likely that IgG receptor on $T\gamma$ cells binds to molecules of each class of IgG. Similarly, $T\alpha$ cells appear to bind to both IgA1 and IgA2 subclasses of the IgA molecules (unpublished observation). $T\mu$ and $T\gamma$ cells have been

extensively studied for the morphological and functional characteristics that will be detailed below.

The 'third' population of lymphoid cells ('null' cells)
Non-T and non-B cells with lymphoid morphology represent a somewhat heterogeneous population of cells. Almost all have high affinity receptors for IgG Fc and approximately two thirds appear to have receptors for EBV and "Ia like" antigens. A very small population also have receptors for C_3. Recently, it has become clear that under appropriate experimental conditions these cells can differentiate into mature erythrocytes, granulocytes, T lymphocytes, or B lymphocytes (74-76). They appear to be heterogeneous and are comprised of progenitor cells committed for various hematopoietic cell lineage; we prefer to call them "unclassified cells."

Functions of lymphocyte subpopulations
Over the past decade progress has been made in the resolution of the multiple genes comprising the major histocompatibility complex or super gene of the mouse (MHC), called the H-2T1a gene complex. The most significant advances in defining the MHC relate to its functional role. It has been established that the gene products of the *K* and *D* region are primary targets for the cell-mediated cytotoxicity reactions in allograft rejection. Recent studies have shown that the most effective cytotoxic reactions against virus infected or chemically modified target cells require *H-2K* and/or *H-2D* identity between the sensitizing cells and the target cell. These findings indicate that these gene products play a direct role in recognition of the target by the effector cell (77,78). At present, it seems certain that this finding reflects the fundamental role of these products in presenting foreign membrane-bound antigens and in mediating an interaction between killer and target cells in immune reactions.

Pilarski (79) has demonstrated that cytotoxic T cells are present as pro-killer cells among the thymocytes of mice. For thymocytes to generate cytotoxic cells, helper T cells appear to be imperative. These helper T cells have some of the same functional properties as T cells, which help B cells to differentiate into antibody-producing plasma cells. The helper cells are antigen-specific, theta bearing, radio resistant, and appear predominantly in spleen. In unprimed situations they do not display strain specificity. Although the mechanism by which helper cells generate killer cells from pro-killer thymocytes is not known, two possibilities must be entertained: 1) helper cells may act on the precursors of T killer cells probably with the help of an accessory cell; or 2) sequential interactions occur in which the helpers act indirectly on the killer precursors by first inducing a pro-helper cell among the thymocyte-derived population to expand clonally and to provide help for the killer precursors also present in thymus. It is of interest that the helper cells that have been irradiated function well in this regard. The genes of the *I* region in mice have been shown to be associated with immunoregulatory activities.

Firm evidence in mice (80) and indirect but convincing evidence in humans (81) indicates that help and suppression are mediated by distinct subsets of T cells each genetically committed to its particular function. In mice, suppressor and helper T cells can be identified by Ly alloantigens present on their surface membranes. In man, these subsets of T lymphocytes have been identified by the presence of different receptors for IgM or IgG on their surface (81). Immunoregulatory T cells may exist as inactive precursors, the pro-helper and pro-suppressor cells (82,83). In human leukemic proliferation, malignant deviation of helper, suppressor, and of pro-suppressor T cells has recently been described (84). These precursors must interact with another set of T cells, the amplifier T cells, before maturing into fully functioning helper or suppressor cells. Immunoregulatory suppressor functions may be antigen-specific or non-specific. The specificity can be directed to either hapten or carrier molecules. In certain systems the effect of suppressor cells on target cells is genetically restricted. Suppressor cells may regulate the production of all immunoglobulin classes (85), a single class of immunoglobulin (86), a single immunoglobulin allotype (87), or a single idiotype (88). In some systems, suppressor cells affect target cells in a genetically restricted fashion; in other systems, no genetic barrier to suppressor cell activity is seen.

In mice it is now possible to define five subregions of the I segment of the H2 complex: I-A, I-B, I-J, I-E, and I-C. I-A subregion codes structural information for a soluble helper T cell factor (83), and other I-subregions participate in suppressor function. Suppressor T cells capable of suppressing MLC release a factor that inhibits the reactivity of responding cells sharing the same I-C subregion genotype (89). The I-J subregion appears to encode genetic information for surface markers found on suppressor T cells and also for the determinants of soluble suppressor factors derived from such cells (90-92). I-J associated suppressor factors are antigen specific and mediate profound suppression of both specific cellular and antibody-mediated responses. In man the genetic control of immunoregulatory functions is largely unexplored. However, Engleman and McDevitt (93) have reported that HLA-D associated gene products can serve as structures permitting T cell subsets to recognize appropriate target cells for exertion of suppressor activity.

Advances in the technology of separating and purifying distinct subpopulations of human lymphocytes have permitted the analysis of the linkage of various functions to T, B, and 'third' (unclassified) populations of lymphoid cells in man (Table II). Discussion of these functions has recently

TABLE II
Functions of Human Lymphocyte Subpopulations

Properties	T Cells	B Cells	"Unclassified" Lymphoid Cells
Proliferative Responses			
Antigen	+	−	−
Allogeneic cells (R)	+	−	−
Allogeneic cells (S)	+S*	+	+
Epstein-Barr Virus	−	+	+
Cytotoxic Responses			
Cell mediated lympholysis	+	−	?
Antibody-dependent cytotoxicity	+S*	−	+
Natural killer activity	+S*	−	+
Mitogen induced cytotoxicity	+	+	+
Lymphokine Production			
Leukocyte migration inhibition factor	+	+	+
Macrophage migration inhibition factor	+	+	+
Blastogenic factor	+	+	+
Lymphotoxin (α)	+	+	+
Interferon	+	+	?
Antibody Synthesis	−	+	+
Miscellaneous			
Precursors of B Cells	−	−	+
Precursors of T cells	−	−	+
Precursors of Granulocytes	−	−	+
Precursors of Erythrocytes	−	−	+

R = Responder
S = Stimulator
S* = Subpopulation

been reviewed in detail (76,94,95). Cells of all three populations respond by proliferation to mitogens (PHA, Con A and PWM), but the degree of proliferative response differs. While proliferative responses to soluble antigens and allogeneic cells in MLC are almost exclusively attributable to T lymphocytes, all three populations produce migration inhibition factors in response to soluble antigens to which the host has been sensitized. Mitogenic factor, interferon and lymphotoxin are all produced by each of the major subsets of lymphocytes. Only T cells have cytotoxic potential in cell-mediated lympholysis. Antibody-dependent cytotoxicity (ADCC) and spontaneous cytotoxicity (SMLC) are mediated by both the 'unclassified' population and by a subset of T cells with IgG (Tγ) receptors.

T cell subpopulations identified by the receptors for immunoglobulin

During the sojourn of thymocytes from thymus to the peripheral blood and the peripheral tissues, mature T cells develop the capacity to express receptors for IgM (Tμ), IgG (Tγ), or IgA (Tα). In addition, a small proportion of T cells in the peripheral blood possess receptors for both IgM and IgG, 'double' receptor, or lack either receptor altogether (Tϕ).

Tμ and Tγ cells have been extensively studied for morphological and functional characteristics (96-99) (Table III). They have distinct morphologic characteristics by both light and electron microscopy (100). Tμ cells are smaller than Tγ cells with higher ratio of nucleus to cytoplasm. They also have smoother surfaces, a less well developed Golgi apparatus, scanty rough endoplasmic reticulum, and paucity of azurophilic granules. By contrast, Tγ cells are equipped with long microvilli, cytoplasm rich in mitochondria, abundant Golgi, and a well developed, rough endoplasmic reticulum. The cytoplasm contains many azurophilic granules that are PAS negative and Alcian blue negative. The RNA content of Tμ and Tγ cells, as measured by flow cytometric analyses, is quite different, as Tμ cells contain approximately twice the amount of RNA as Tγ cells (101).

Table IV shows the tissue distribution of T cell subsets in various lymphoid compartments (17, 18). Peripheral blood, cord blood and tonsils have comparable proportions of Tμ

TABLE III

Characteristics of Human T Cell Subpopulations

Characteristics	Tμ Cells	Tγ Cells
B cell differentiation	↑s	↓s
T cell proliferation	?	↓s
Natural Killer activity	−	+s
Antibody-dependent cytotoxicity	−	+s
Blastogenic responses to:		
Phytohemagglutinin	+	−
Concanavalin A	+	+
Allogeneic cells	+	+
Mediator Production:		
Migration inhibition factor (LMIF)	+	−
Interferon	+	+
Adherence to nylon, wool or plastic	−	+s
Locomotor properties	+	−
Histamine receptors	−	+s
Thymopoietin	−	↑
Corticosteroids	−	+
Irradiation	−	+
Sensitivity to: Pronase	+	±
Trypsin	+	−
Neuraminidase	+	−
RNA content	high	low
Morphology: Nuclear:cytoplasmic ratio	high	low
Golgi body	rich	few
Rough endoplasmic reticulum	abundant	scanty
Cytoplasmic granules	+	−
α-nephthyl acetate esterase	+	−

s = subpopulation
↑ = enhancement
↓ = inhibition

and Tγ cells, while lymph nodes contain low proportions of Tα cells and no Tγ cells. The spleen is rich in Tγ cells and contains low proportions of both Tμ and Tα cells. Thymocytes, in general, lack all Tμ, Tγ and Tα phenotypes.

These figures suggested to us that T cell subsets might have different locomotor properties. Using modified Boyden chamber assay and bovine casein as a chemoattractant, we demonstrated that Tμ cells migrate well into the filters, whereas Tγ cells either migrated poorly or did not migrate at all (102). Further, when T cell subpopulations are isolated by density gradient electrophoresis according to their surface charge, Tμ cells were enriched in the high mobility fractions and Tγ cells in low mobility fractions (103).

T cell subsets demonstrate differential sensitivities to corticosteroid, irradiation, and the inductive influence of thymopoietin (104). Tγ cells are radiosensitive, while Tμ cells are radioresistant. Tγ cells are suppressed in vitro by high doses of corticosteroids, but this susceptibility varies among different normal individuals, and the concentrations of corticosteroids required for the effect cannot be reached during therapy in patients. Tμ cells, by contrast, are totally resistant to the effect of any reasonable concentration of corticosteroids. Thymopoietin pentapeptide increases the proportion of Tγ cells after incubation with peripheral blood T cells in vitro, which suggests that a population of precursor Tγ cells exists in the peripheral blood that can be induced to differentiate to Tγ cells.

Recently, we have analyzed the presence of receptors for histamine on T cell subsets. Using histamine-coated sepharose bead coluns, we demonstrated that histamine receptors are present as a subset of Tγ cells but almost completely absent from Tμ cells (105).

Moretta, et al (106) examined the proliferative responses of Tμ and Tγ cells to PHA and Con A. Tμ and Tγ cells responded similarly to different concentrations of Con A, both in their peak proliferative response and in the kinetics of their response. Tγ cells, however, did not respond to PHA. In contrast, Tμ cells responded with the same peak proliferative response as that of unseparated T cells but required much higher concentrations of PHA to achieve that response. In our own study of proliferative responses in one way MLC, both the Tμ and Tγ populations responded similarly to allogeneic stimulator cells.

Tμ and Tϕ cells produced leukocyte migration inhibition factor (LMIF) in response to PHA or Con A in amounts comparable to that produced by unfractionated T cells (107). In contrast, Tγ cells either failed to produce LMIF or produced less LMIF than that of Tμ cells.

Moretta, et al (81) have also examined the functional properties of Tμ and Tγ cells in immunoregulation of B cell differentiation to plasma cells following stimulation with pokeweed mitogen (PWM). When Tμ cells were added to B cells and cultured in the presence of PWM, differentiation of B cells to plasma cells occurred. This reaction indicated that Tμ cells may act as helper T cells. In contrast, when Tγ cells were added to B cells along with PWM, no differentiation to plasma cells was observed, suggesting that Tγ cells are not helper T cells. However, when Tγ cells were added to cultures of B cells, Tμ cells and PWM, no differentiation of B cells to plasma cells was observed. These experiments led these investigators to conclude that Tμ cells are helpers and Tγ cells are suppressors. Later, it became clear that neither of these populations in their entirety are helpers or suppressors. Hayward, et al (108) demonstrated that Tμ cells after activation with Con A could suppress differentiation of B cells to plasma cells. In another study, such an effect was associated with change in surface phenotype (Tμ → Tγ) of a subpopulation of Tμ cells (109). These experiments indicate that the Tμ cell population is heterogeneous. Similarly, we have demonstrated that it is only a subpopulation of Tγ

TABLE IV

Distribution of T Cell Subsets

Lymphoid Compartment	$T\mu$(%) Mean ± SD	$T\gamma$(%) Mean ± SD	$T\alpha$(%)	Mean ± SD
Peripheral Blood (60)	52.2 ± 10.8	10.4 ± 4.0	(15)	8.2 ± 4.6
Cord Blood (24)	46.0 ± 9.8	22.2 ± 6.0	(4)	4.2 ± 2.2
Tonsils (8)	54.0 ± 15.0	6.4 ± 4.0	(6)	9.4 ± 3.2
Bone Marrow (4)	55.0 ± 23.8	8.5 ± 4.4		Not Done
Thymus (8)	2.1 ± 3.5	3.1 ± 3.2	(2)	0.0
Spleen (4)	10.4 ± 2.4	48.0 ± 10.2	(4)	2.4 ± 1.2
Lymph Nodes (8)	49.0 ± 6.0	1.6 ± 2.0	(4)	2.2 ± 1.6

( ) = number of specimens examined

cells (histamine receptor positive) that mediates suppression of either T or B cell responses (105).

Recently, we have reported (110) that both T and non-T cells can mediate ADCC and natural killer (nk) activity. Among the T cells, both ADCC and nk activity are present in $T\gamma$ cells and absent from $T\mu$ cells. Histamine receptor negative $T\gamma$ cells appear to participate in the killer activity (unpublished observations). Clear but indirect evidence both in animals and humans suggests that the T cell mediating ADCC activity is distinct from that mediating nk.

The analysis of these two subpopulations, both for their numbers and proportions in the peripheral blood and lymphoid organs of patients with primary and secondary immunodeficiency disorders, demonstrates that an imbalance among two subsets and maldistribution among lymphoid compartments are frequently encountered in primary and secondary immunodeficiency disorders (111-116).

Recently, it has been demonstrated that the T cell subsets, particularly $T\gamma$ cells, undergo changes in their surface phenotypes and show modulation of their functions as well (110,117), although these changes occur only when insoluble immune complexes (OxRBC-IgG) are used to isolate them from non-$T\gamma$ cells. It is unclear whether these changes occur in vivo in pathologic states associated with circulating soluble immune complexes. If this were the case, analysis of T cell subsets employing the use of Fc receptors would be less useful. However, when we used sera from patients with connective tissue diseases who have high levels of circulating soluble immune complexes, we could not observe a shift of phenotype or modulation of their functions, e.g., ADCC (unpublished observation). Therefore, the influence of soluble immune complexes in vitro does not correlate with that influence in vivo.

Summary

From the accumulating data, it is evident that T lymphocytes are at least as heterogenous as B lymphocytes. We can now visualize the immune system as having not only two arms but also hands and fingers which work together in a splendid, highly coordinated fashion. Furthermore, it appears likely that several more populations of T and B lymphocytes will be discovered in the future. It will be important to define the function(s) of each new subpopulation to determine how its functions integrate with the other subpopulations before immune systems can be understood as a single functional unit.

References

1. Owen JJT. The origins and development of lymphocyte populations. In: Porter R, Knight J, eds. Ontogeny of acquired immunity. Amsterdam: Associated Scientific Publisher, 1972:35.
2. Wybran J, Carr MC, Fudenberg HH. Effect of serum on human rosette-forming cells in fetuses and adult blood. Clin Immunol Immunopath 1973;1:408.
3. Stites DP, Caldwell JP, Carr MC, Fudenberg HH. Ontogeny of immunity in humans. Clin Immunol Immunopath 1975;4:519.
4. Dwyer JM, Warner NL, McKay IR. Specificity and nature of the antigen-combining sites of fetal and mature thymus lymphocytes. J Immunol 1972;108:1439.
5. Kay HEM, Doe J, Hocklay A. Response of human foetal thymocytes to phytohemmagglutinins. Immunology 1970;18:393.
6. Papiernik M. Correlation of lymphocyte transformation and morphology in the human fetal thymus. Blood 1970;36:470.
7. Playfair JHL, Woldendale MR, Kay HEM. The leucocyte of peripheral blood in human foetus. Br J Hematol 1963;9:336.
8. August CS, Berkel AE, Driscott S, Merler E. Ontogeny of lymphocyte function in the developing human fetus. Ped Red 1971;5:539.
9. Stites DP, Carr MC, Fudenberg HH. Ontogeny of cellular immunity in human fetus. Development of responses to phytohemagglutinin and to allogeneic cells. Cell Immunol 1976;11:257.
10. Carr MC, Stites DP, Fudenbery HH. Dissociation of responses to phytohemmagglutinin and adult allogeneic lymphocytes in human foetal lymphoid tissues. Nature (New Biol) 1973;241:279.

11. Stites DP, Carr MC, Fudenberg HH. Development of cellular immunity in human fetus: Dichotomy of proliferative and cytotoxic responses of lymphoid cell to phytohemagglutinin. Proc Natl Acad Sci 1972;69:1440.

12. Asantila T, Sorvari T, Hirvonen J, Toiramen P. Xenogeneic reactivity of human fetal lymphocytes. J Immunol 1973;111:984.

13. Touraine JL, Hadden JW, Good RA. Sequential stages of human T lymphocyte differentiation. Proc Natl Acad Sci 1977;74:3414.

14. Touraine JL. A model of sequential differentiation and ontology of T lymphocytes in man. In: B Serrou, C Rosenfeld, eds. Human lymphocyte differentiation: Its application to cancer. North-Holland Amsterdam: North-Holland Biomed Press 1978:93.

14a. Hirano T, Kishimoto T, Kuritani T, Muraguchi A, Yamamura Y, Ralph P, Good RA. In vitro immune response of human peripheral blood lymphocytes. IV. Specific induction of human suppressor T cells by an antiserum to the T leukemia cell lines HSB. J Immunol 1979;23:1133.

15. Raisner Y, Biniaminor M, Rosenthal E, Sharon N, Ramot B. Interaction of peanut agglutinin with normal human lymphocytes and leukemic cells. Proc Natl Acad Sci 1979;76:447.

16. Vogler LB, Crist WM, Bockman DE, Pearl ER, Lawton AR, Cooper MD. Pre-B cell leukemia: A new phenotype of childhood lymphoblastic leukemia. N Eng J Med 1978;298:872.

17. Gupta S, Good RA. Subpopulations of human T lymphocytes. III. Quantitation and distribution in peripheral blood, cord blood, tonsils, bone marrow, thymus, lymph nodes and spleen. Cell Immunol 1978;36:363.

18. Gupta S, Platsoucas CD, Schulof RS, Good RA. Receptors for IgA on subpopulations of human T and B lymphocytes. Cell Immunol 1979;45:469.

19. Gupta S, Good RA. Human T cell subpopulations as defined by Fc receptors. Thymus 1979;1:135.

20. Raff MC, Megson M, Owen JJT, Cooper MD. Early production of intracellular IgM by B lymphocyte precursors in mouse. Nature 1976;259:224.

21. Gelfand MC, Elfebein GJ, Frank MM, Paul WE. Ontogeny of B lymphocytes. II. Relative rates of appearance of lymphocytes bearing surface immunoglobulin and complement receptors. J Exp Med 1974;139:1125.

22. Nossal GJV, Pike BL. Studies on the differentiation of B lymphocytes in the mouse. Immunology 1973;25:33.

23. Hayward AR, Simons M, Lawton AR, Cooper MD, Mage RG. Pre-B and B cells in rabbits. Fed Proc 1977;36:1295.

24. Gathings WE, Lawton AR, Cooper MD. Immunofluorescent studies of the development of Pre-B cell, B lymphocyte and immunoglobulin isotype diversity in humans. Eur J Immunol 1977;7:804.

25. Vossen JM, Hijman SW. Membrane associated immunoglobulin determinants on bone marrow and blood lymphocytes in the pediatric age group and in fetal tissues. Ann NY Acad Sci 1975;254:262.

26. Gupta S, Pahwa R, O'Reilly RJ, Good RA, Siegal FP. Ontogeny of lymphocyte subpopulations in human fetal liver. Proc Natl Acad Sci 1976;73:919.

27. Ishizaka K, Ishizaka T, Okudaira H, Bazin H. Ontogeny of IgE bearing lymphocytes in the rat. J Immunol 1978;120:655.

28. Gupta S, Grieco MH. Rosette formation with mouse erythrocytes. I. A probable marker for human B lymphocytes. Int Arch Allergy Appl Immunol 1975;49:734.

29. Gupta S, Good RA, Siegal FP. Rosette formation with mouse erythrocytes. II. A marker of human B and non-T lymphocytes. Clin Exp Immunol 1976;25:319.

30. Stathopoulos A, Elliott EV. Formation of mouse or sheep red blood cell rosettes by lymphocytes from normal and leukemic individuals. Lancet 1974;1:600.

31. Gupta S, Good RA, Siegal FP. Rosette formation with mouse erythrocytes. III. Studies in primary immunodeficiency and lymphoproliferative disorders. Clin Exp Immunol 1976;26:204.

32. Koziner B, Filippa D, Mertelsmann R, Gupta S, Clarkson B, Good RA, Siegal FP. Characterization of malignant lymphomas in leukemic phase by multiple differentiation markers of mononuclear cells. Correlation with clinical features and conventional morphology. Am J Med 1977;63:556.

33. Froland SS, Natvig JB. Class, subclass and allelic exclusion of membrane bound Ig on human B lymphocytes. J Exp Med 1972;136:609.

34. Fu SM, Winchester RJ, Kunkel HG. Occurrence of surface IgM, IgD and free light chains on human lymphocytes. J Exp Med 1974;139:451.

35. Natvig JB, Salsano F, Froland SS, Seavem P. Membrane IgD and IgM on single cell carry same idiotype. In: Seligmann M, Preud'Homme JL, Kourilsky FM, eds. Membrane receptors of lymphocytes. Amsterdam: North-Holland Biomed Press, 1975:13.

36. Burgois A, Abney ER, Parkhouse RE. Mouse immunoglobulin receptors on lymphocytes: Identification of IgM and IgD molecules by tryptic cleavage and a postulated role for cell surface IgD. Eur J Immunol 1977;7:210.

37. Arbeit RD, Henkart PA, Dickler HB. Differences between Fc receptors of two lymphocyte subpopulations of human peripheral blood. Scand J Immunol 1977;6:873.

38. Wisloff F, Froland SS. Antibody-dependent lymphocyte-mediated cytotoxicity in man. No requirement for lymphocytes with membrane bound immunoglobulins. Scand J Immunol 1973;2:151.

39. Bianco C, Patrick R, Nussenzweig V. A population of lymphocytes bearing a membrane receptor for antigen-antibody-complement-complexes. I. Separation and characterization. J Exp Med 1970;132:702.

40. Ross GD, Polley MJ, Rabellino E, Grey HM. Two different complement receptors on human lymphocytes. One specific for C_3b and one specific for C_3b inactivator-cleaved C_3b. J Exp Med 1973;138:798.

41. Bokish VA, Sobel AT. Receptor for the fourth component of complement on human B lymphocytes and cultured human lymphoblastoid cells. J Exp Med 1974;140:1334.

42. Sobel AT, Bokish VA. Receptors for C_4b and C_1q on human peripheral lymphocytes and lymphoblatoid cells. In: Seligmann M, Peud'Homme JL, Kourilsky FM, eds. Membrane receptors of lymphocytes. New York: American Alsevier, 1975:151.

43. McConnell I, Lachmann PJ. Complement and cell membranes. Transp Rev 1976;32:72.

44. Bernard A, Boumsell L, Good RA. Complement inhibitors released from leucocytes. II. Evidence that lymphocytes release and produce an inhibitor of C_2 activation. Cell Immunol 1976;22:351.

45. Brown JC, DeJesus DG, Holborow EJ, Harris G. Lymphocyte-mediated transport of aggregated α-globulin into germinal center areas of normal mouse spleen. Nature 1970;228:367.

46. Mitchell J, Abbott A. Ultrastructure of the antigen-retaining reticulum of lymph node follicles as shown by high-resolution autoradiography. Nature 1965;208:500.

47. Nossal GJV, Abbott A, Mitchell J, Lummus Z. Antigenic immunity: XV. Ultrastructural features of antigen capture in primary and secondary lymphoid follicles. J Exp Med 1968;127:277.

48. Jondal M, Klein G. Surface markers on human T and B lymphocytes II. Presence of Epstein-Barr virus receptors on B lymphocytes. J Exp Med 1973;138:1365.

49. Greaves MF, Brown G, Rickinson A. Receptors for Epstein-Barr virus on human B lymphocytes. Clin Immunol Immunopath 1975;3:514.

50. Wernet P, Winchester R, Kunkel HG. Serological detection and partial characterization of human MLC determinants with special reference to B cell specificity. Tranplant Proc (Suppl 1) 1975;7:193.

51. Winchester RJ, Meyers PA, Broxmeyer HE, Wang CY, Moore MAS, Kinkel HG. Inhibition of human erythropoietic colony formation in culture by treatment with Ia antisera. J Exp Med 1978;148:613.

52. Winchester JR, Ross GD, Jarowski CI, Broxmeyer HE. Expression of Ia-like antigen molecules on human granulocytes during early phases of differentiation. Proc Natl Acad Sci 1977;74:4012.

53. Samarut C, Gebuhrer L, Brochier J, Betrel J, Revillar JP. Presence of "Ia like" antigens on human T lymphocytes bearing receptors for IgG. Eur J Immunol 1977;7:908.

54. Touraine JL, Touraine F, Kiszkiss DF, Choi YS, Good RA. Heterologous specific antiserum for identification of human T lymphocytes. Exp Immunol 1974;16:502.

55. Hammerstrom S, Hellstrom U, Perlmann P, Dillner ML. A new surface marker on T-lymphocytes of human peripheral blood. J Exp Med 1973;138:1270.

56. Hellstrom U, Perlmann P, Robertson ES, Hammerstrom S. Receptors for Helix promatia A hemagglutinin (HP) on a subpopulation of human B cells. Scand J Immunol 1978;7:191.

57. Hellstrom U, Mellstedt H, Perlmann P, Holm G, Patterson D. Receptors for Helix promatia A (HP) hemagglutinin on leukemic lymphocytes from patients with chronic lymphocytic leukemia (CLL). Clin Exp Immunol 1976;26:196.

58. Ranki A, Tolterman TH, Hayry P. Identification of resting human T and B lymphocytes by acid α-naphthyl acetate esterase staining combined with rosette-formation with staphylococcus aureus Strain Cowan I. Scand J Immunol 1976;5:1129.

59. Tolterman TH, Ranki A, Hayry P. Expression of the acid α-naphthyl acetate esterase marker by activated and secondary T lymphocytes in man. Scand J Immunol 1977;6:305.

60. Knowles DM, Hoffman T, Ferrarini M, Kunkel HG. The demonstration of acid α-napthyl acetate esterase activity in human lymphocytes: Usefulness as a T cell marker. Cell Immunol 1978;35:112.

61. Evans RL, Bread JM, Lazarus H, Schlossman SF, Chess L. Defection of two human T cell subclasses bearing unique differentiation antigens. J Exp Med 1977;145:221.

62. Evans RL, Lazarus H, Penta AC, Schlossman SF. Two functionally distinct subpopulations of human T cells that collaborate in the generation of cytotoxic cells responsible for cell-mediated lympholyses. J Immunol 1978;120:1423.

63. Dickler HB, Adkinson NF, Terry WD. Evidence for individual human peripheral blood lymphocytes bearing both B and T cell markers. Nature 1974;247:213.

64. Hallberg T, Gurner BW, Coombs RRA. Opsonic adherence of sensitized ox red cells to human lymphocytes as measured by rosette-formation. Int Arch Allergy Appl Immunol 1973;44:500.

65. Ferrarini M, Moretta L, Abrile R, Durante ML. Receptors for IgG molecules on human lymphocytes forming spontaneous rosettes with sheep red cells. Eur J Immunol 1975;5:70.

66. Chiao JW, Good RA. Studies of the presence of membrane receptors for complement, IgG and human lymphocytes. Eur J Immunol 1976;6:157.

67. Moretta L, Ferrarini M, Durante ML, Mingari MC. Expression of a receptor for IgM by human T cells *in vitro*. Eur J Immunol 1975;5:565.

68. McConnell I, Hurd CM. Lymphocyte receptors. II. Receptors for rabbit IgM on human T lymphocytes. Immunology 1976;30:835.

69. Lum LG, Muchmore AV, Keren D, Dicker J, Koski I, Strober W, Blaese RM. A receptor for IgA on human T lymphocytes. J Immunol 1979;122:65.

70. Strelkauskas AJ, Schauf V, Wilson BS, Chess L, Scholossman SF. Isolation and characterization of naturally occurring subclasses of human peripheral blood T cells with regulatory functions. J Immunol 1978;120:1278.

71. Strelkauskas AJ, Callery RT, McDowell J, Borel Y, Schlossman SF. Direct evidence for loss of human suppressor cells during active autoimmune disease. Proc Natl Acad Sci 1978;75:5150.

72. Conradie JD, Bubb MD. CH_4 domain of IgM has cytophilic activity for human lymphocytes. Nature 1977;265:160.

73. Preud'Homme JL, Gonnot M, Tspais A, Brouet JC, Minaesco C. Human T lymphocyte receptors for IgM. Reactivity with monomeric 8S subunits. J Immunol 1977;119:2206.

74. Richmann CM, Chess L, Yankee RA. Purification and characterization of granulocyte progenitor cells (CFu-c) from human peripheral blood using immunologic surface markers. Blood 1978;51:1.

75. Nathan DG, Chest L, Hillman DG, Clarke B, Breard J, Merler E, Housman DE. Human erythroid burst-forming unit. T cell requirement for proliferation *in vitro*. J Exp Med 1978;147:324.

76. Chess L, Schlossman SF. Functional analysis of distinct human T cell subsets bearing unique differentiation antigens. Contemp Top Immunobiol 1977;7:363.

77. Doherty PC, Blanden RV, Zinkernagel RM. Specificity of virus-immune effector T cells for H-2K or H-2D compatible interactions: Implications for H-antigen diversity. Transplant Rev 1976;29:89.

78. Shearer GM, Rehn TG, Schmitt-Verchulst AM. Role of the murine major histocompatibility complex in the specificity of *in vitro* T cell-mediated lympholysis against chemically-modified autologous lymphocytes. Transplant Rev 1976;29:222.

79. Pilarski LM. A requirement for antigen-specific helper T cells in the generation of cytotoxic T cells from thymoctyte percursors. J Exp Med 1977;145:709.

80. Cantor H, Boyse E. Regulation of the immune response by T-cell subclasses. Contemp Top Immunobiol 1977;7:47.

81. Moretta L, Webb SR, Grossi CE, Lydyard PM, Cooper MD. Functional analysis of two human T cell subpopulations help and suppression of B-cell responses by T cells bearing receptors for IgM or IgG. J Exp Med 1977;146:184.

82. Feldmann M, Beverley PCL, Wood J, McKenzie FS. T-T interactions in the induction of suppressor and helper T cells: Analysis of membrane phenotype of precursor and amplifier cells. J Exp Med 1977;145:793.

83. Tada T, Taniguchi M, Okumura M. Regulation of antibody response by antigen-specific T-cell factors bearing I region determinants. Prog Immunol 1977;3:364.

84. Broder S, Poplak D, Whang Feng J, Dwim M, Goldman C, Muul L, Waldmann TA. Characterization of a suppressor-cell leukemia; Evidence for the requirement of an interaction of two T cells in the development of human suppressor effector cell. N Engl J Med 1978;298:66.

85. Waldmann TA, Broder S, Blaese RM, Durm M, Blackman M, Strober W. Role of suppressor T cells in pathogenesis of common variable hypogammaglobulinemia. Lancet 1974;2:609.

86. Atwater JS, Tomasi TB. Suppressor cells and IgA deficiency. Clin Immunol Immunopath 1978;9:379.

87. Herzenberg LA, Okumura K, Metzler CM. Regulation of immunoglobulin and antibody production by allotype suppressor T cells in mice. Transplant Rev 1975;27:57.

88. Rajewsky K, Eichmann K. Antigen receptor of T helper cells. Contemp Top Immunobiol 1977;7:113.

89. Rich SS, Rich RR. Regulatory mechanisms in cell-mediated immune response. III. I-region control of suppressor cell interaction with responder cells in mixed lymphocyte reactions. J Exp Med 1976;143:672.

90. Green MI, Pierres A, Dorf ME, Benacerrof B. The I-J subregion codes for determinants on suppressor factor(s) which limit the contract sensitivity response to picryl chloride. J Exp Med 1977;146:293.

91. Theze J, Watenbaugh C, Dorf M, Benacerrof B. Immunosuppressive factor(s) specific for 1-glutamic acid[50], L-tyrosne[50] (GT). II. Presence of I-J determinants on the GT-suppressive factor. J Exp Med 1977;146:287.

92. Tada T, Taniguchi M, David CS. Properties of the antigen-specific suppressive T-cell factor in the regulation of antibody response of the mouse. VI. Special subregion assignment of the gene(s) that codes for the suppressive T-cell factor in the H-2 histocompatibility complex. J Exp Med 1976;144:713.

93. Engleman EG, McDevitt HO. A suppressor T cell of the mixed lymphocyte reaction specific for the HLA-D region in man. J Clin Invest 1978;61:828.

94. Gupta S, Good RA. Lymphocyte subpopulation and functions in hypersensitivity disorders. In: Cellular molecular and clinical aspects of allergic disorders. Gupta S, Good RA, eds. New York: Plenum Press, 1979:87.

95. Gupta S, Kapoor N. Lymphocyte subpopulations: Surface, intracellular enzymatic markers and functions. In: Infections complicating the abnormal host. Grieco MH, ed. New York: Yorke Medical Book, 1980 (in press).

96. Gupta S, Good RA. Human T cell subsets in health and disease. In: Human lymphocyte differentiation: Its application to cancer. Serru B, Rosenfeld C, eds. Amsterdam: North Holland Biomed Press, 1978:367.

97. Gupta S. Functionally distinct subpopulations of human T lymphocytes. Clin Bull 1978;8:100.

98. Gupta S, Good RA. Subpopulations of human T lymphocytes as defined by Fc receptors. Thymus 1979;1:135.

99. Gupta S. T cell subpopulations: Structure, functions, and profile in normals and patients with primary immunodeficiency lymphoproliferative and autoimmune disorders. Pol Arch Wein Med 1979;61:161.

100. Grossi CE, Webb SR, Zicca A, Lydyard PM, Moretta L, Mingari MC, Cooper MD. Morphological and histochemical analysis of two human T-cell subpopulations bearing receptors for IgM or IgG. J Exp Med 1977;147:1405.

101. Andreeff M, Beck JD, Darzynkiewicz Z, Traganos F, Gupta S, Melamed MR, Good RA. RNA content in human lymphocyte subpopulations. Proc Natl Acad Sci 1978;75:1938.

102. Parrott DMV, Good RA, O'Neill GJ, Gupta S. Heterogeneity of locomotion of human T cell subsets. Proc Natl Acad Sci 1978;75:2392.

103. Platsoucas CD, Good RA, Gupta S. Separation of human T cell subpopulations ($T\mu$, $T\gamma$) by density gradient electrophoresis. Proc Natl Acad Sci 1979;76:1972.

104. Gupta S, Good RA. Subpopulations of human T lymphocytes. II. Effect of thymopoietin corticosteroids, and irradiation. Cell Immunol 1977;34:10.

105. Rocklin RE, Breard J, Gupta S, Good RA, Melmon KL. Characterization of the human blood lymphocytes that produce a histamine-induced suppressor factor (HSF). Cell Immunol (in press).

106. Moretta L, Ferrarini M, Mingari MC, Moretta A, Webb S. Subpopulations of human T cells identified by receptors for immunoglobulins and mitogen responsiveness. J Immunol 1976;17:2171.

107. Kapadia A, O'Reilly RJ, Good RA, Gupta S. Leukocyte migration inhibition factor (LMIF) production by human T cell subpopulation. Fed Proc 1978;37:1365.

108. Hayward AR, Layward L, Lydyard PM, Moretta L, Dagg M, Lawton AR. Fc receptor heterogeneity of human suppressor T cells. J Immunol 1978;121:1.

109. Gupta S, Schwartz SA, Good RA. Subpopulations of human T lymphocytes. VIII. Cellular basis of Con A-induced T cell-mediated suppression of immunoglobulin production by B cells from normal humans. Cell Immunol 1979;44:242.

110. Gupta S, Fernandes G, Nair M, Good RA. Spontaneous and antibody-dependent cell-mediated cytotoxicity by human T cell subpopulations. Proc Natl Acad Sci 1978;75:5137.

111. Gupta S, Good RA. Subpopulation of human T lymphocytes. I. Studies in immunodeficient patients. Clin Exp Immunol 1977;30:222.

112. Gupta S, Kapadia A, Kapoor N, Good RA. Immunoregulatory T lymphocytes in patients with primary immunodeficiency disorders. Ind J Med Res 1979;69:645.

113. Gupta S, Good RA. Subpopulations of human T lymphocytes. V. T lymphocytes with receptors for immunoglobulin M or G in patients with primary immunodeficiency disorders. Clin Immunol Immunopath 1978;11:292.

114. Gupta S, Good RA. Subpopulations of human T lymphocytes. IV. Distribution and quantitation in patients with mycosis fungoides and Sezary syndrome. Cell Immunol 1978;39:18.

115. Gupta S, Malaviya AN, Rajgopalan P, Good RA. Subpopulations of T lymphocytes. IX. Imbalance of T cell subpopulations in patients with progressive systemic sclerosis. Clin Exp Immunol 1979;38:342.

116. Gupta S, Tan C, Good RA. Locomotion of T cells and distribution of T cell subsets in childhood Hodgkin's disease. Fed Proc 1979;38:1162.

117. Pichler WJ, Lum L, Border S. Fc receptors on human T lymphocytes. I. Transition of $T\gamma$ cells to $T\mu$ cells. J Immunol 1978;121:1540.