0031-6997/82/3401-0017$02.00/0
PHARMACOLOGICAL REVIEWS

Vol. 34, No. 1
Printed in U.S.A.

The Characterization and Function of Human Immunoregulatory T Lymphocyte Subsets*

ELLIS L. REINHERZ AND STUART F. SCHLOSSMAN

Division of Tumor Immunology, Sidney Farber Cancer Institute and the Department of Medicine, Harvard Medical School, Boston, Massachusetts

Functional T lymphocyte subpopulations can be identified in humans by antibodies which detect stable glycoprotein antigens on their surface. Thus, inducer T lymphocytes bear an antigen termed T4 while suppressor T lymphocytes bear an antigen termed T5. Immune homeostasis results from a delicate balance between inducer and suppressor subsets within the T-cell circuit and perturbation in subset dynamics may initiate a wide variety of immunopathological disorders. Here Ellis Reinherz and Stuart Schlossman discuss the present understanding of this circuit, its role in the pathogenesis of a number of diseases, and how the human immune response can be manipulated in an orderly way through modulation of selected T-cell subsets.

THE PRECISE dissection of cellular mechanisms and interactions involved in the generation of human T-cell responses has been facilitated in recent years by advances in four areas: 1) the development of *in vitro* methods for the characterization and identification of human T-lymphocyte subsets by cell-surface markers; 2) the development of new techniques for the isolation of highly purified subclasses of human T lymphocytes dependent on cell surface markers; 3) the development of *in vitro* techniques to discriminate functional properties and interactions of the isolated subsets of T lymphocytes and other cells (that is, B cells, null cells, and macrophages); and 4) the capacity to correlate normal and abnormal functional properties of T-lymphocyte subpopulations *in vitro* with *in vivo* disorders of the immune response. These advances have enabled us to throw light on the major T-lymphocyte subsets in man and their unique functional programs.

The genetic program of the human T lymphocyte is complex, including immunoregulation as well as the capacity to recognize specific antigens and execute unique effector functions. Thus, T lymphocytes proliferate in response to soluble and cell-surface antigens and polyclonal activators, including the mitogens phytohemagglutinin (PHA) and concanavalin A (con A) (1, 2). They are responsible for cytotoxic killer activity in cell-mediated lympholysis (CML) (3) and produce a host of soluble factors (4, 5) which effect a variety of cellular functions. Perhaps more importantly T lymphocytes are involved in virtually all regulatory interactions including helper and suppressor-cell functions (6, 7).

In this review, we will focus upon the recent developments in our understanding of the differentiation of T lymphocytes and their functional maturation. We will also provide evidence that during differentiation, T cells diverge into functionally distinct subsets, programmed for their respective inducer (helper) and cytotoxic/suppressor functions, which can be defined by unique cell-surface glycoprotein antigens.

Differentiation of T Lymphocytes

A thymic micro-environment is necessary for the differentiation of T cells in all species. It appears that precursor bone-marrow cells (prothymocytes) migrate to the thymus gland, where they are processed, become functionally competent, and are exported into the peripheral lymphoid compartment (8–11). Moreover, profound changes in cell-surface antigens mark the stages of T-cell ontogeny (12–13).

In man the earliest lymphoid cells within the thymus lack mature T-cell antigens but bear antigens shared by bone-marrow cells of several lineages (14). This population accounts for approximately 10% of thymic lymphocytes and is reactive with two monoclonal antibodies, anti-T9 and anti-T10 (stage I). Although these two antibodies are not specific for T cells (11–15) (since they react with normal, activated and malignant cells of non-T lineages), they are useful in providing an understanding of antigenic changes that occur during T-cell ontogeny. With maturation, thymocytes lose T9, retain T10, and acquire a thymocyte-distinct antigen defined by anti-T6. Concurrently, these cells express antigens defined by anti-T4 and anti-T5/T8 (stage II). The T4+, T5+/8, T6+ and T10+ thymocytes account for approximately 70% of the total thymic population. With further maturation, thymocytes lose the T6 antigen, express T1 and T3 antigens to the full, and segregate into T4+ and T5+* subsets (stage III). Immunological competence is ac-

* Reprinted from *Immunology Today*, April, 1981, pp. 69–75, with the kind permission of the publisher, Elsevier/North-Holland Biomedical Press, Cambridge. The article covers the material presented by Dr. Schlossman at the Workshop.

* $T5^+$ cells also express T8 antigen. For simplification, however, these cells are referred to as $T5^+$ rather than $T5^+/8^+$.

TABLE 1
*Monoclonal antibodies to human T cell surface antigens**

Monoclonal Antibodies	Approximate Molecular Weights of Antigens[25–30]		Cell Surface Expression (% Reactivity with Antibodies)			Trade Designations[a]
	Non-reduced	*Reduced*	*Thymocytes*	*T Cells*	*Non-T cells*	
Anti-T1[b]	69K	69K	10[c]	100	0	OKT1, Leul
Anti-T3	19K	19K	10[c]	100	0	OKT3, Leu4
Anti-T4	62K	62K	75	60	0	OKT4, Leu3a/Leu3b
Anti-T5	76K	30K + 32K	80	25	0	OKT5
Anti-T8	—	—	80	30	0	OKT8, Leu2a/Leu2b
Anti-T6[d]	49K	49K	70	0	0	NAI/34 OKT6
Anti-T9[b]	190K	94K	10	0	0	OKT9, 5E9
Anti-10[b]	37K	45K	95	5	10	OKT10

* Reproduced with permission from *Immunology Today*, April 1981, Elsevier/North-Holland Biomedical Press, Cambridge.

[a] OK designations are available through Ortho Pharmaceuticals, Raritan, NJ. Leu designations are available through Becton-Dickinson, Mountain View, CA. 5E9 is available through NIAID monoclonal antibody serum bank, Bethesda, MD. NAI/34 is available through Accurate Chemical, NJ.

[b] T9 and T10 antigens are not T lineage specific and are found on normal and malignant populations of non-T cells (14–15). In addition, both antigens are expressed on a fraction of peripheral T cells following mitogen stimulation (27).

[c] 10% of thymocytes express a high density of T1 and T3 antigens while the remaining thymocytes express little or faint reactions with anti-T1 and anti-T3 (22).

[d] T6 is B_2-microglobulin associated.

quired at this stage but is not fully developed until the thymic lymphocytes are exported (16). Outside the thymus the resting (T1+, T3+, T4+) and (T1+, T3+, T5+) subsets lack T10 and represent the circulating inducer (helper) (17, 18) and cytotoxic/suppressor populations (19, 20, 21), respectively.

Unlike the majority of the thymocytes which express little or only faint reactivity with anti-T1 and anti-T3 (22), all of the circulating peripheral T cells are strongly T1+ and T3+. The T4 antigen is expressed on approximately 55–65% of peripheral T cells, and the T5 (18) antigen is present on 20–30%. These two subsets correspond to TH_2– helper and TH_2+ cytotoxic/suppressor cells, respectively (19, 23). Moreover, unlike stage II thymocytes, T4 and T5/T8 antigens are expressed on mutually exclusive subsets of mature T cells (14, 20, 24). Table I lists the cell-surface expression of antigens defined by monoclonal antibodies and shows their preliminary biochemical characterization (25–30).

Functions of Mature T Lymphocyte Subsets

Given the existence of two distinct subpopulations of peripheral T cells and the multiplicity of functional responses effected by T lymphocytes, it is important to determine whether an individual T lymphocyte possesses all these effector and regulatory functions or whether T cells within a subset are unique with respect to their functional repertoire. A series of functional studies on isolated subpopulations of peripheral T lymphocytes has demonstrated that the latter hypothesis is correct and that the specific program of T cells is linked to the expression of a particular cell-surface antigen.

For example, only the T1+, T3+, T4+ population responded to soluble antigen (17). In contrast, both subsets of cells show a maximal response to cell surface antigens (alloantigens). In additional studies, it was shown that the T1+, T3+, T4+ population responds maximally to PHA, while the T1+, T3+, T5+ subset showed a diminished response. Both cell populations respond similarly to conA.

As mentioned above, one of the major effector functions of human T lymphocytes is their capacity to become sensitized to HLA-A, -B, and -C locus antigens and to effect specific cell-mediated killing. It was found that only the T1+, T3+, T5+ subset (20, 24) contained a cytotoxic effector population when separated after allogeneic activation in mixed lymphocyte culture. The T1+, T3+, T4+ population, although capable of proliferating to alloantigen, did not become cytotoxic when separated after sensitization (17).

Perhaps the most important difference between these T-cell subsets was evident from their differential regulatory effects on the immune response (6, 7). The T1+, T3+, T4+ cells were shown to provide inducer (helper) function in the T-T, T-B, and T-macrophage interactions. For example, although the T1+, T3+, T4+ cells were not cytotoxic effectors when separated after allogeneic stimulation, they were required for optimal development of cytotoxicity within the T1+, T3+, T5+ effector population (17). This is similar to findings in previous studies which showed that the TH_2+ population defined by heteroantisera contained the cytotoxic effector cell, while the TH_2– population contained the helper cell for development of cytotoxicity (23).

Thus the T1+, T3+, and T4+ (T4+) T cells provided an inducer function in T-T interactions. T4+ T cells also provided helper function in T-B interactions (18, 21). Only the T4+ T-cell subset provided the signals necessary to help autologous B cells to proliferate and differentiate into immunoglobulin-containing cells. In contrast, the T1+, T3+, T5+ (T5+) T cells did not induce B cells to proliferate or to differentiate. Moreover, the inducer role of the T4+ T cells for B-cell immunoglobulin production was shown in both a pokeweed-mitogen-stimulated (18) and an antigen-stimulated system (31).

Prior studies demonstrated that antigen-triggered T

cells produced helper factors, including lymphocyte mitogenic factor (4) (which induced proliferation of T cells, B cells, null cells, and macrophages) and T-cell replacing factor which initiated B-cell immunoglobulin synthesis in the absence of T cells. In recent studies, it was found that only the T4+ subset made these nonspecific helper factors (31). The T-cell subset restriction of these factors in man further stresses the importance of this T-cell subset to the induction of the human immune response.

The above findings helped assign an inducer role to the T4+ population in T-T, T-B, and T-macrophage interactions. Moreover, they provided additional evidence that a proliferative response to soluble antigen is restricted to the inducer population. The regulatory effects of the T4+ population do not appear limited to cells of lymphoid lineage. Since it is known that antigen-stimulated T lymphocytes produce helper factors which modulate erythroid stem-cell production *in vitro*, it is probable that the T4+ population of lymphocytes is important in some aspect of erythroid differentiation (32). Similarly, osteoclast-activating factor (33) and soluble factors inducing fibroblast proliferation and collagen synthesis have been shown to be derived from antigen-stimulated T lymphocytes (34). These findings suggest a much broader biological role for the T4+ inducer population in man. In contrast, the T5+ subset contains a mature population of cells with cytotoxic and suppressor function but not inducer function (20–21). Following activation with conA, T5+ cells suppressed autologous T cells responding in mixed lymphocyte culture (MLC). In addition, this same T5+ population suppressed B-cell immunoglobulin production. It should be emphasized at this point that although both T4+ and T5+ subpopulations proliferated equally well on mitogenic stimulation by con A, only the T5+ population became suppressive. These results support the view that the T4+ and T5+ subpopulations have a separate program for their respective helper and suppressor functions independent of that required to discriminate and react to nonspecific polyclonal mitogens or antigens. Moreover, these results suggest that the programming of the specific cell function is linked to the expression of a particular cell-surface phenotype and that such programming occurs before cell activation.

Further evidence substantiating this notion is provided by the subsets' differential susceptibility to expression of Ia antigens following specific activation stimuli (35). In several species, immunoregulatory activities are mediated by intercellular signals involving products of the I region of the major histocompatibility complex. Human Ia-like antigens were first defined by alloantisera (36) and subsequently by heteroantisera (37) and monoclonal antibodies (35). In man, Ia antigens are expressed on the surface of B cells, most monocytes and a subset of null cells, but are not detected on resting T cells (35, 38). Activation of human T cells results in *de novo* biochemical synthesis and cell-surface expression of Ia antigens (39). Thus, the appearance of Ia antigen on T-cell subsets serves as a marker of specific T-cell activation. Following alloactivation in MLC or stimulation by PHA and con A, both T4+ and T5+ T-cell subsets express Ia antigens. In contrast, when the T-cell population is specifically activated by soluble antigens, only the T4+ subset expresses Ia. Therefore, the appearance of Ia antigens on unique T-cell subsets depends on the activation stimuli and the ability of that individual subset to respond to a given stimulus.

The observation that only a fraction (~40%) of T4+ T cells expressed Ia antigen on activation suggested that the T4+ population might be heterogeneous. To test this possibility, antigen-activated T4+ T cells were separated into T4+Ia+ and T4+Ia− populations and characterized (40). It was found that the T4+Ia+ population contained the majority of proliferating T cells and that most of this proliferation was non-specific. Elimination of the T4+Ia+ T-cell subset with monoclonal anti-Ia+ and complement treatment, diminished subsequent proliferation to the triggering antigen and to unrelated antigens. In addition, only the antigen induced T4+Ia+ subset produced non-specific helper factors. Although the Ia− fraction represents 60% of the T4+ population it showed minimal proliferation to soluble antigen and did not elaborate helper factors. Nonetheless, a mixture of both T4+Ia+ and T4+Ia− T cells was required for maximal Ig secretion by B cells, since these two T4+ subsets worked in a synergistic fashion.

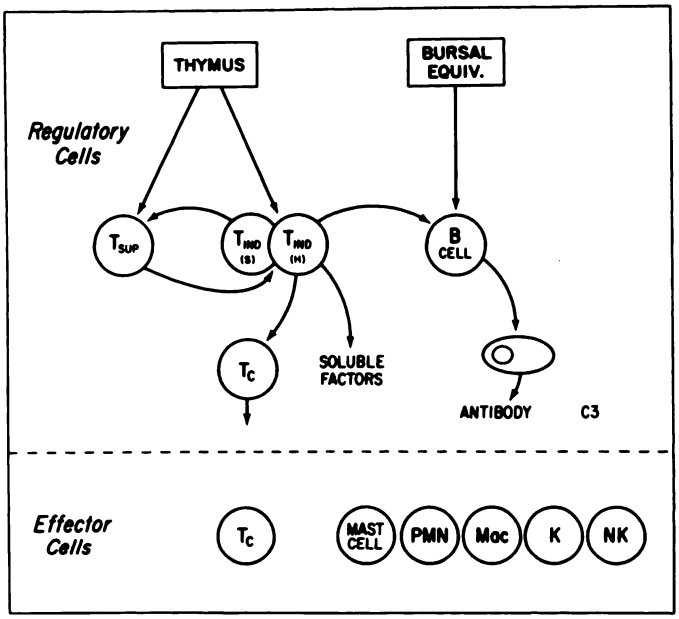

FIG. 1. The human T-cell circuit. Cellular and humoral responses are regulated by $T4^+$ inducer (Tind) and $T5^+$ suppressor (Tsup) T lymphocytes. One subpopulation of $T4^+$ cells ($Tind_{(S)}$), reactive with JRA autoantibodies, induces $T5^+$ suppressor cell activation while a second subpopulation of $T4^+$ cells ($Tind_{(H)}$) induces help for cytotoxic T cell (Tc) effector function, B cell differentiation and immunoglobulin production. Many of the effector cells illustrated above including NK, K, mast cells, polymorphonuclear leukocytes (PMN) and macrophages (Mac) are under the influence of these regulatory cells and their products. (Reproduced with permission from *Immunology Today*, April 1981, Elsevier/North-Holland Biomedical Press, Cambridge.)

Other studies have provided additional evidence to support the existence of heterogeneity within the T4+ subset. It was shown that approximately 35% of T4+ T cells and 10% of T5+ cells reacted with an antibody found in the serum of many patients with active juvenile rheumatoid arthritis (41). These T4+JRA+ cells, are required to induce the T5+ subset to mediate suppression of B-cell Ig secretion. Thus T4+JRA+ T cells appear to be the inducer cells of suppression while T4+JRA$^-$ cells are the T inducers of help (fig. 1). Yet to be determined is the relationship of T4+Ia+ lymphocytes to the T4+JRA+ subset.

Therefore the T4+ subset is analogous to the murine Ly1+2 subset which provides helper function through both specific and non-specific signals and induces suppressor cell activation as well (42). In this regard the T4+JRA+ subset has a counterpart in the Lyt1+Qal+ murine subpopulation (43) and the T4+Ia+ in the Lyt1+2$_1$Ia+ subset (44). The T5+ T subset in man appears to be analogous to the murine Lyt2,3+ subset which mediates both cytotoxic and suppressor functions (42). Based on the evolutionary conservation of other cell-surface molecules (that is, immunoglobulins, MHC-encoded antigens, etc.), it is likely that the antigens defining the phenotypes of inducer and suppressor populations in man and mouse are biochemically similar. There is already good evidence to indicate that the T5 antigen and the Lyt2,3 antigen are homologous (27). However, whether the T4 antigen and the Lyt1 antigen are similar is less certain. Nonetheless, given the observation that T4 and T5 are on reciprocal subsets in man with similar functions to the murine Lyt1+2 and Lyt2+ populations it is likely that an antigen equivalent to T4 exists on a murine Lyt1+2 subset.

Clinical Disorders of T Lymphocytes

In this review, we have provided evidence to support the theory that it is possible to detect T-lymphocyte subpopulations with unique biological functions on the basis of their cell-surface antigenic components. The application of this technology to human immunodiagnosis is just beginning. It is now possible to define the heterogeneity of T-cell malignancies; diseases of T-cell maturation and/or premature release; diseases associated with loss of T cells; diseases associated with imbalances of T-cell subset restricted functions; and diseases associated with activation of T-cell subsets.

Since immunological functions are acquired only at the latest stage of intrathymic ontogeny, premature release of immunologically incompetent cells or aberrations of T-cell maturation resulting in blocked differentiation could lead to immunodeficiency. The development of probes that make it possible to define points along the differentiative pathway should help in the understanding of heterogeneity within congenital immunodeficiencies. In this regard it has already become evident that patients with severe combined immunodeficiency may have thymocytes blocked in differentiation either at stage I (T10+ or T9+T10+) or stage III (T3+T4+T5+/T8+T10+) (45). As expected, only those patients with the latter population express any T-cell function (i.e. MLC proliferation).

Major immunological abnormalities result from alterations in the mature T cell subsets. Some patients with acquired agammaglobulinemia lack the T4+ population and possess a T cell population incapable of triggering B cell synthesis of immunoglobulin. This specialized circumstance must be discriminated from that in the majority of patients with agammaglobulinemia, who have B-cell abnormalities but possess normal T cells (6, 7).

Circulating activated T4+ cells appear to result in different immunopathological abnormalities including the formation of autoantibodies directed at red cells, white cells, and platelets. Activated helper cells have been demonstrated in patients with active graft-v.-host disease (46), and similar abnormalities have been seen in patients with sarcoid, scleroderma, and Sjogren's syndrome. Not only is there an increase in T4+ cells, but these activated T lymphocytes, unlike resting lymphocytes, express Ia-like (HLA-D related) antigens. The presence of activated T lymphocytes in human disease is not uncommon (47). Whether activated T4+T cells account for hyperglobulinemia, lymphocytosis, dermal infiltration, granuloma formation, or fibrotic lesions in the diseases mentioned above is being investigated.

It is obvious that defects in immunoregulation could result from either a loss or a persistent activation of the T5+ population. Loss of the T5+ T cells should result in unopposed inducer functions, whereas activated T5+ cells should suppress the immune response. In patients with acute graft-v.-host disease, in which activated helper cells have been demonstrated there is also a loss of suppressor cells (46). A similar loss of T5+ cells has been seen in naturally occurring autoimmune diseases including systemic lupus erythematosus (48), hemolytic anemia (49), multiple sclerosis (50), severe atopic eczema, hyper-IgE syndrome and inflammatory bowel disease (7). Moreover, the loss of the T5+ population may correlate temporally with the severity of clinical disease. The precise mechanism by which one population is lost or another activated is not clear. There is evidence from patients with lupus that autoantibodies are present in the serum and directed at the T5+ population (51). Autoantibodies may selectively eliminate the suppressor population or modulate its functional properties. Similarly, in studies of patients with juvenile rheumatoid arthritis, the loss of suppressor cell function correlates with increased B cell Ig secretion, the presence of autoantibodies to a T4+ subset which induces suppressor cell function, and increased disease activity (41).

In contrast, the presence of excessive numbers of activated suppressor cells results in severe immunodeficiency. For example, in a small number of patients with acquired agammaglobulinemia, activated T5+, Ia+ cells were responsible for suppressing autologous B cell pro-

duction of immunoglobulin (49). Increased numbers of activated suppressor cells have also been seen after viral infections including those caused by Epstein-Barr virus and cytomegalovirus (52). In infectious mononucleosis, the self-limited increase in suppressor cells may account for transient immunologic hyporesponsiveness, but in patients with chronic graft-v.-host disease, persistent circulating suppressor cells cause prolonged immunologic incompetence (46). Moreover, antigen-specific suppressor cells may result in human disorders. Patients with lepromatous leprosy have a T5+ population that can be specifically activated by lepromin (53). In this case, activation of T5+ T cells is antigen-specific; nevertheless, these activated suppressor cells may cause generalized immunosuppression. Presumably, the energy seen in tuberculosis, systemic fungal infections, and protozoan infections may result from similar mechanisms. Finally it should be noted that an imbalance in the inducer:suppressor cell ratio is itself sufficient to result in diminished immunoglobulin production *in vitro* and agammaglobulinemia *in vivo*. A relative increase in suppressor cells is a common finding in patients with acquired agammaglobulinemia and circulating B cells (48).

Human T-Cell Malignant Diseases

The ability to define cell-surface antigens that appear at specific stages of T-cell differentiation has, in addition, allowed for the orderly dissection of T-cell malignant processes in human beings. In fact, these T-cell diseases reflect the same degree of heterogeneity and maturation as is seen in normal T-cell ontogeny (14). For example, the tumor cells in most cases of acute T-cell lymphoblastic leukemia arise from an early thymocyte or prothymocyte compartment (stage I), whereas in only 20% of cases the cells are derived from a common (stage II) thymocyte compartment and therefore bear the T6 antigen. To date, we have found only one T-cell acute-lymphoblastic-leukemia tumor that arose from the most mature thymic compartment and expressed the T3 antigen (stage III). Since normal thymocytes have not acquired mature T-cell functions at either the level of the stage I or II thymocytes, it is not surprising that the vast majority of acute lymphoblastic leukemia T cells in human beings have no demonstrable function.

The tumor populations from patients with T-cell chronic lymphocytic leukemia, Sezary syndrome and mycosis fungoides are derived from the mature T cell compartment bearing the T1 or T3 antigens or both (15, 54). Therefore, as expected some of these tumor cells display helper or suppressor functions. In this regard all tumor populations from patients with Sezary syndrome bear the T1+T3+T4+ phenotype and may demonstrate the functional capacity to provide help for B cell Ig synthesis. T cell CLL tumor populations have mature inducer or suppressor phenotypes. Since 6 of 8 T-CLL tumor populations studied to date have been of the helper phenotype, it would appear that the frequency of subset deri-

vation corresponds to that expected from the normal ratio of inducer:suppressor cells (i.e. 2–3:1).

Immunotherapy by Selective T-Cell Subset Manipulation

The ability to dissect normal lymphoid differentiation and define the biology of lymphocytes in health and disease will allow an understanding of the disorders of the human immune response. In addition to their immunodiagnostic utility, the reagents described in this review may be potent therapeutic tools themselves. It is also likely that certain drugs will have selective effects on individual T-cell subsets such that they could be utilized to alter the ratio of T inducer and T suppressor cells.

Finally, it is important to note that anti-T3 may serve as an important immunosuppressive agent since anti-T3 alone was found in earlier studies to block proliferative responses of T lymphocytes to both soluble and cell surface antigens (55). As few as 10^4 molecules of anti-T3 per cell appeared to inhibit these responses when added early in the culture period.

In addition to abrogating antigen-stimulated T cell proliferation responses, anti-T3 blocked the ability of T cells to provide help to autologous B lymphocytes in a T-dependent, PWM-driven system. Thus, in the presence of anti-T3, Ig secretion by the T-B mixture was reduced to the level of Ig secretion found in B cells. Similar to the inhibition of T cell proliferation, anti-T3 inhibition of PWM-driven Ig secretion occurred during an early phase of cell-cell interaction. The ability of anti-T3 to inhibit T-cell proliferation as well as T-B co-operation suggests that anti-T3 defines an important T cell interaction molecule. The failure of all other T cell specific antibodies to block these functions and the fully developed expression of the T3 antigen late in thymic differentiation, at the time of acquisition of immunologic competence, suggests the importance of T3 (55).

Given the potency and specificity of monoclonal antibodies compared with conventional heteroantisera and non-specific immunosuppressive agents one would predict that reagents of this type should be useful in treatment of autoimmune disorders as well as in renal and bone marrow transplantation. Indeed anti-T3 has already proved useful in preventing and abrogating renal allograft rejection in human beings. (Personal communication, Renal Transplant Group, Mass. General Hospital.) We believe that recent advances in the understanding of human immunology as outlined in this review suggest strategies with which to manipulate the immune response for the benefit of the host.

REFERENCES

1 Chess, L., MacDermott, R. P., and Schlossman, S. F.: J. Immunol. **113**:1113–1121, 1979.
2 Chess, L., MacDermott, R. P., and Schlossman, S. F.: J. Immunol. **113**:1122–1127, 1979.
3 Sondel, P. M., Chess, L., MacDermott, R. P., and Schlossman, S. F.: J. Immunol. **114**:982–987, 1975.

4 GEHA, R. S., SCHNEEBERGER, E., ROSEN, F. S., AND MERLER, E.: J. Exp. Med. **138**:1230–1247, 1973.
5 ROCKLIN, R. E., MACDERMOTT, R. P., CHESS, L., SCHLOSSMAN, S. F., AND DAVID, J. R.: J. Exp. Med. **140**:1303–1316, 1974.
6 REINHERZ, E. L., AND SCHLOSSMAN, S. F.: Cell **19**:821–827, 1980.
7 REINHERZ, E. L., AND SCHLOSSMAN, S. F.: N. Engl. J. Med. **303**:370–373, 1980.
8 MOORE, M. R. S., AND OWEN, J. J. T.: J. Exp. Med. **126**:715–725, 1967.
9 OWEN, J. T. T., AND RITTER, M. A.: J. Exp. Med. **129**:431–437, 1969.
10 OWEN, J. T. T., AND RAFF, M. C.: J. Exp. Med. **132**:1216–1232, 1970.
11 STUTMAN, O., AND GOOD, R. A.: Transplant. Proc. **3**:923–925, 1971.
12 RAFF, M. C.: Transplant. Rev. **6**:52–80, 1971.
13 KONDA, S., STOCKERT, E., AND SMITH, R. T.: Cell. Immunol. **7**:275–289, 1973.
14 REINHERZ, E. L., KUNG, P. C., GOLDSTEIN, G., LEVEY, R. H., AND SCHLOSSMAN, S. F.: Proc. Natl. Acad. Sci. U.S.A. **77**:1588–1592, 1980.
15 REINHERZ, E. L., AND SCHLOSSMAN, S. F.: Cancer Res., in press.
16 REINHERZ, E. L., KUNG, P. C., GOLDSTEIN, G., AND SCHLOSSMAN, S. F.: J. Immunol. **123**:1312–1317, 1979.
17 REINHERZ, E. L., KUNG, P. C., GOLDSTEIN, G., AND SCHLOSSMAN, S. F.: Proc. Natl. Acad. Sci. U.S.A. **76**:4061–4065, 1979.
18 REINHERZ, E. L., KUNG, P. C., GOLDSTEIN, G., AND SCHLOSSMAN, S. F.: J. Immunol. **123**:2894–2896, 1979.
19 REINHERZ, E. L., AND SCHLOSSMAN, S. F.: J. Immunol. **122**:1335–1341, 1979.
20 REINHERZ, E. L., KING, P. C., GOLDSTEIN, G., AND SCHLOSSMAN, S. F.: J. Immunol. **124**:1301–1307, 1980.
21 REINHERZ, E. L., MORIMOTO, C., PENTA, A. C., AND SCHLOSSMAN, S. F.: Eur. J. Immunol. **10**:570–572, 1980.
22 BHAN, A. K., REINHERZ, E. L., POPPEMA, S., MCCLUSKEY, R., AND SCHLOSSMAN, S. F.: J. Exp. Med. **152**:771–782, 1980.
23 EVANS, R. L., LAZARUS, H., PENTA, A. C., AND SCHLOSSMAN, S. F.: J. Immunol. **120**:1423–1428, 1978.
24 REINHERZ, E. L., HUSSEY, R. E., AND SCHLOSSMAN, S. F.: Immunogenetics **11**:421–426, 1980.
25 VAN AGTHOVEN, A., TERHORST, C., REINHERZ, E. L., AND SCHLOSSMAN, S. F.: Eur. J. Immunol, in press.
26 MARTIN, P. J., HANSON, J. A., NOWINSKI, R. C., AND BROWN, M. A.: Immunogenetics, in press.
27 TERHORST, C., VON AGTHOVEN, A., REINHERZ, E. L., AND SCHLOSSMAN, S. F.: Science **209**:520–521, 1980.
28 TERHORST, C., VON AGTHOVEN, A., LE CLAIR, K., SNOW, P., REINHERZ, E. L., AND SCHLOSSMAN, S. F.: Cell, in press.
29 MCMICHAEL, A. J., PILCH, J. R., GALFRE, G., MASON, D. Y., FABRE, J. W., AND MILSTEIN, C.: Eur. J. Immunol. **9**:205–210, 1979.
30 LEDBETTER, J., EVAN, R. L., LIPINSKI, M., CUNNINGHAM-RUNDLES, C., GOOD, R. R., AND HERZENBERG, L. A.: J. Exp. Med., in press.
31 REINHERZ, E. L., KUNG, P. C., BREARD, J. M., GOLDSTEIN, G., AND SCHLOSSMAN, S. F.: J. Immunol. **124**:1883–1887, 1980.
32 LIPTON, J. M., REINHERZ, E. L., KUDISCH, M., JACKSON, P. L., SCHLOSSMAN, S. F., AND NATHAN, D. G.: J. Exp. Med. **152**:350–360, 1980.
33 HORTON, J. E., RAIZA, L. G., SIMMONS, H. A., OPPENHEIM, J. J., AND MORGENHAGEN, S. E.: Science **177**:793–795, 1972.
34 COHEN, S., PICK, E., AND OPPENHEIM, J. J.: *In* Biology of the Lymphokines Academic Press, New York, 1979.
35 REINHERZ, E. L., KUNG, P. C., PESANDO, J. M., RITZ, J., GOLDSTEIN, G., AND SCHLOSSMAN, S. F.: J. Exp. Med. **150**:1472–1482, 1979.
36 WINCHESTER, R. J., FU, S. M., WERNET, P., KUNDEL, H. G., DUPONT, B., AND JERSILD, C.: J. Exp. Med. **141**:924–929, 1975.
37 HUMPHREY, R. E., MCCUNE, J. M., CHESS, L., HERRMAN, H. D., MALENKA, D. J., MANN, D. L., PARHAM, P., SCHLOSSMAN, S. F., AND STROMINGER, J. L.: J. Exp. Med. **144**:98–112, 1976.
38 SCHLOSSMAN, S. F., CHESS, L., HUMPHREYS, R. E., AND STROMINGER, J. L.: Proc. Natl. Acad. Sci. U.S.A. **73**:1288–1292, 1976.
39 EVANS, R. L., FALDETTA, T. J., HUMPHREYS, R. E., PRATT, D. M., YUNIS, E. J., AND SCHLOSSMAN, S. F.: J. Exp. Med. **148**:1440–1445, 1978.
40 REINHERZ, E. L., MORIMOTO, C., PENTA, A. C., AND SCHLOSSMAN, S. F.: J. Immunol, in process.
41 MORIMOTO, C., REINHERZ, E. L., BOREL, Y., MANTZOURAIS, E., STEINBERG, A. D., AND SCHLOSSMAN, S. F.: J. Clin. Invest., in press.
42 CANTOR, H., AND BOYSE, E. H.: Cold Spring Harbor Symp. Quart. Biol. **41**:23–32, 1977.
43 EARDLEY, D. D., HUGENBERGER, J., MCVAY-BOUDREAU, L., SHEN, F. W., GERSHON, R. K., AND CANTOR, H.: J. Exp. Med. **147**:1106–1115, 1978.
44 KELLER, D. M., SWIERHOSZ, J. E., MARROCK, P., AND KAPPLER, J. W.: J. Immunol. **124**:1350–1359, 1980.
45 REINHERZ, E. L., SCHLOSSMAN, S. F., AND ROSEN, F. S.: Unpublished results.
46 REINHERZ, E. L., PARKMAN, R., RAPPAPORT, J. M., ROSEN, F. S., AND SCHLOSSMAN, S. F.: N. Engl. J. Med. **300**:1061–1068, 1979.
47 YU, D. T. Y., WINCHESTER, R. J., FU, S. M., GIBOFSKY, A., KO, H. S., AND KUNKEL, H. G.: J. Exp. Med. **151**:91–100, 1980.
48 MORIMOTO, C., REINHERZ, E. L., STEINBERG, A. D., SCHUR, P. H., MILLS, J. A., AND SCHLOSSMAN, S. F.: J. Clin. Invest. **66**:1171–1174, 1980.
49 REINHERZ, E. L., RUBINSTEIN, A., GEHA, R. S., ROSEN, F. S., AND SCHLOSSMAN, S. F.: N. Engl. J. Med. **301**:1018–1022, 1979.
50 REINHERZ, E. L., WEINER, H. L., HAUSER, S. L., COHEN, J. A., DISTASO, J., AND SCHLOSSMAN, S. F.: N. Engl. J. Med. **303**:125–129, 1980.
51 MORIMOTO, C., REINHERZ, E. L., ABE, T., HOMMA, M., AND SCHLOSSMAN, S. F.: Clin. Immunol. Immunopathol. **16**:474–484, 1980.
52 REINHERZ, E. L., O-BRIEN, C., ROSENTHAL, P., AND SCHLOSSMAN, S. F.: J. Immunol. **125**:1269–1274, 1980.
53 MEHRA, V., MASON, L. H., ROTHMAN, W., REINHERZ, E. L., SCHLOSSMAN, S. F., AND BLOOM, R. R.: J. Immunol. **125**:1183–1198, 1980.
54 BOUMSELL, L., BERNARD, A., REINHERZ, E. L., NADLER, L. M., RITZ, J., COPPIN, H., RICHARD, Y., DUBERTRET, L., DEGOS, L., LEMERLE, J., FLANDRIN, G., DAUSSET, J., AND SCHLOSSMAN, S. F.: Blood, in press.
55 REINHERZ, E. L., HUSSEY, R. E., AND SCHLOSSMAN, S. F.: Eur. J. Immunol. **10**:758–762, 1980.