MEDICAL GRAND ROUNDS

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IMMUNODEFICIENCY IN THE ADULT

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SUMMARY

IMMUNODEFICIENCY IN THE ADULT

In a rapidly expanding discipline such as Immunology, it is difficult to place in perspective its proper impact in biology in general and in clinical medicine in particular. That immunologic competence bestows on mammalian organisms the capacity to fend off repeated infections with pathogenic organisms is well recognized, and preventive immunization procedures are commonplace. An important role for immunologic responsiveness in the pathogenesis of many acute and chronic inflammatory diseases of man also seems solidly established and extends to the acceptance, albeit grudgingly, of the existence of auto-immune diseases. But the immunologist's appetite is voracious and insatiable, and within the recent past such diverse afflictions of mankind as malignancy (1,2) and aging (3) itself have been claimed to be partly or completely on an immunologic basis. While such claims may be dismissed as rubbish, their projection by famous and respected scientist/clinicians demands that the ideas receive careful consideration.

In an effort to sort out sense from nonsense, it is essential that an approach to immunologic competence in the adult be formulated so that the relevance of immunologic deficiency to the various afflictions of man can be rationally considered. The capacity to respond immunologically to new and native antigens must be described, validated and quantified with the hope that two goals will be reached: first, that the immunologic basis for certain human diseases can be identified and verified rather than vaguely surmised, and second, that patterns and mechanisms of deficiency can be established which can then be attacked by the new therapeutic discipline of immunotherapy.

The concept of immunologic deficiency disorders was ushered into clinical medicine by the original observations of Bruton (4) and then championed by the elegant and percipient work of Robert Good and his colleagues (5,6). The patient material from which this early work was derived was drawn from a predominately pediatric population and as a consequence the approach to classification and description of immunodeficiency disorders in man has been from the developmental standpoint. In fact, the close similarities between the ontogenetic and phylogenetic development of the immune system have provided mutually supporting proof for the well-accepted current view of the division of the immune system into two components parts: a thymus-dependent portion consisting of thymus influenced lymphocytes, primarily responsible for the generation of cell-mediated immunity, and a bursal-dependent portion consisting of B lymphocytes which give rise, generally with the aid of T lymphocytes, to antibody forming cells. This now familiar organization of the immune system is displayed in Figure 1 (7). Based on this scheme, a classification of the Primary Immunodeficiency Disorders in Man has been established by the World Health Organization (8) and is presented in Table 1. The asterisks placed on the table have been added to indicate which of the disorders are seen with any substantive frequency in adults. This extremely useful classification of immunodeficiency disorders is applicable to a Pediatric medical practice, but is virtually useless for adult patients, and that comes as no surprise. The immunodeficiency disorders in adults emerge in individuals who have apparently gone through a perfectly normal developmental sequence and who possess, or at least at an earlier time did possess, a normal functioning thymus, bursal-equivalent, and stem cell producing site. Thus, it requires that a different mode of classification be employed in order to make sense of the array of immunodeficiency disorders in adults.

A reasonable approach to this issue would seem to be to use as a launching point, a consideration of the mature, intact immunologic response which can be set awry in a variety of ways. The immunologic reflex arc has been a useful model with

Figure 1.

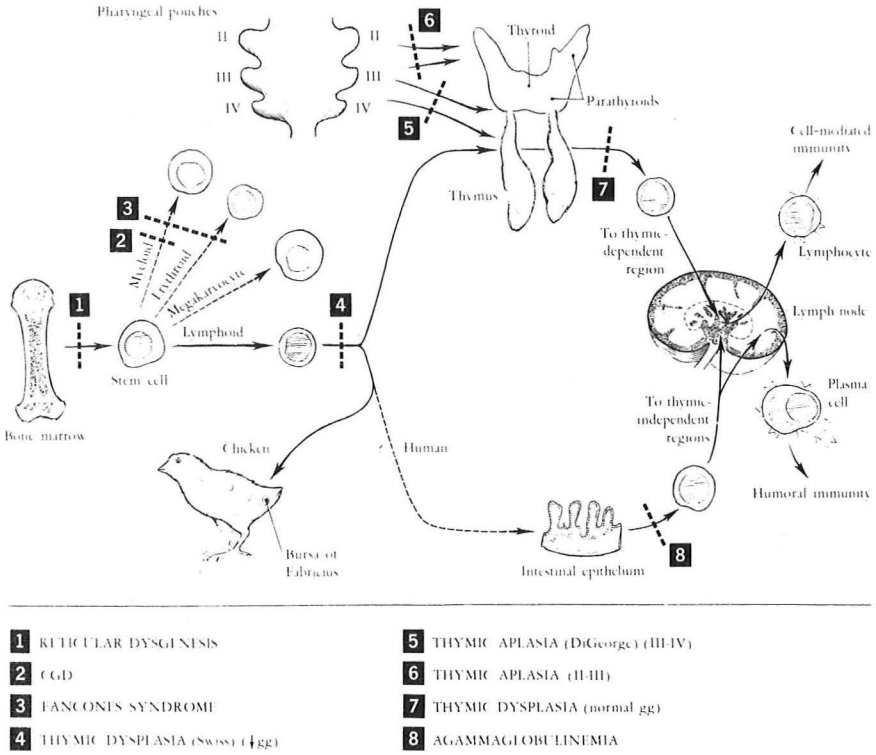


Table I.
Classification of Primary Immunodeficiency Disorders

Type	Suggested Cellular Defect: B-Cells	T-Cells	Stem Cells
Infantile X-linked agammaglobulinemia	+		
Selective immunoglobulin deficiency (IgA)*	+		
Transient hypogammaglobulinemia of infancy	+		
X-linked immunodeficiency with hyper-IgM	+	?	
Thymic hypoplasia		+	
Episodic lymphopenia with lymphocytoxin		+	
Immunodeficiency with normal or without hyper-immunoglobulinemia*	+	+/-	
Immunodeficiency with ataxia-telangiectasia	+	+	
Immunodeficiency with thrombocytopenia and exzema (Wiskott-Aldrich syndrome)	+	+	
Immunodeficiencywith thymoma	+	+	
Immunodeficiency with short-limbed dwarfism	+	+	
Immunodeficiency with generalized hematopoietic hypoplasia	+	+	+
Severe combined immunodeficiency			
(a) autosomal recessive	+	+	+
(b) X-linked	+	+	+
(c) sporadic	+	+	+
Variable immunodeficiency (common)*	+	+/-	

*Disorders seen in adults

which to analyze the immune response and has been chosen as the basis for this discussion of Immunodeficiency in the adult. The immunologic reflex arc will be defined and described in the first section of this presentation; in the second section, mechanisms of disrupting the successful completion of the arc will be outlined; next, the diagnostic laboratory approach to documenting clinical immunodeficiency resulting from disruption of the arc will be presented; and finally, the Immunodeficiency disorders of adults will be classified and discussed in terms of pathogenesis according to the reflex analogy.

IMMUNOCOMPETENCE AND THE IMMUNOLOGIC REFLEX ARC

The notion that the mature immunologic response to an antigen is analogous to a neural reflex stems from the realization that in normal individuals the application of an appropriate antigenic stimulus regularly leads to a predictable and consistent immunologic response. The analogy to a spinal reflex can be further extended by arbitrarily dividing the immunologic reflex into three components: an afferent limb, a central processing mechanism, and an efferent limb. This analogy has turned out to be extremely useful in the experimental laboratory as a means of studying the intricacies of immune responses. Similarly, it offers a rational basis on which to consider the pathogenesis and expression of immunodeficiency as it appears in adult human beings.

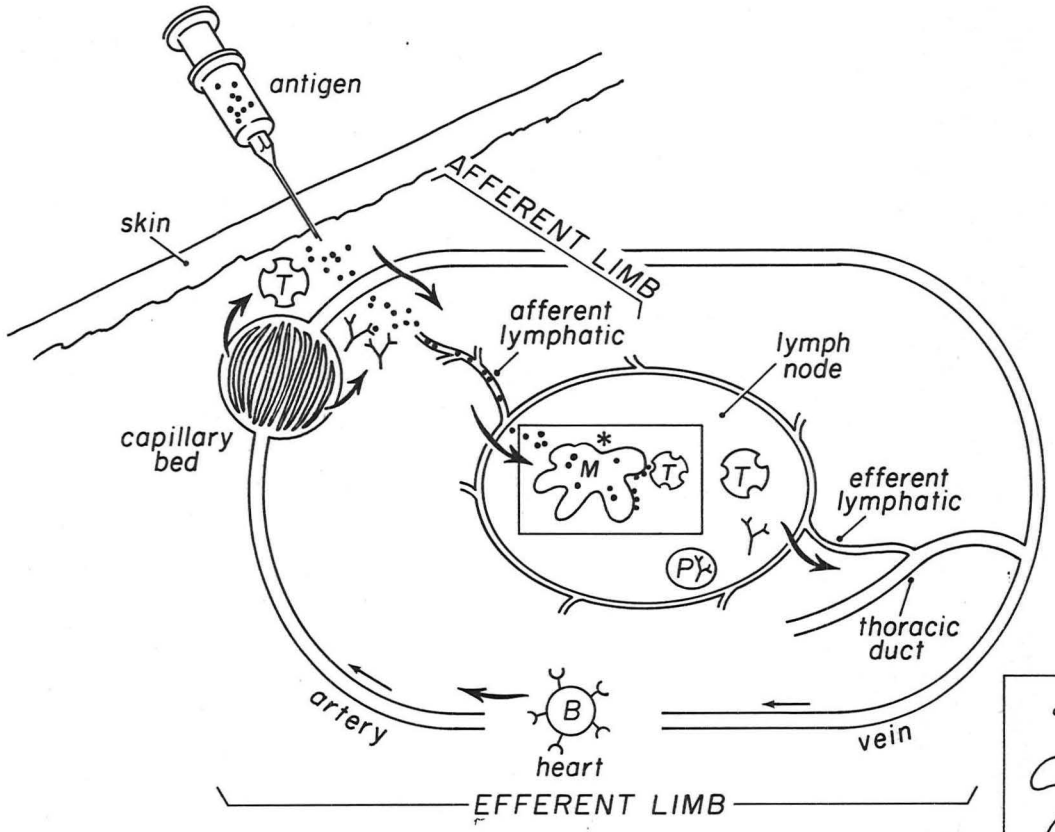
The Afferent Limb

The afferent limb of the reflex arc encompasses that interval between exposure of the host to a new antigen and the moment at which recognition of that antigen by an immunocompetent cell has taken place (see Figure 2). For parenterally administered antigens, it is required that the antigen gain access to a competent lymphoid organ (lymph nodes, spleen, Peyer's patch, etc) either via lymphatic or venous routes. Antigen is therein taken up and processed by macrophages and reticulum cells which in turn present the focused antigenic determinants to lymphocytes capable of recognizing those determinants by specific receptors present on their plasma membrane. It is the engagement of antigen with the membrane receptor of the antigen reactive lymphocyte that completes the afferent limb of the immunologic reflex arc and simultaneously provides the signal for the subsequent events of division and differentiation which constitute the central processing mechanism. Thus the requirements for an intact afferent limb are antigen, specific antigen reactive cells, functional macrophages residing in an immunocompetent lymphoid organ with an intact lymphatic and/or venous vascular supply.

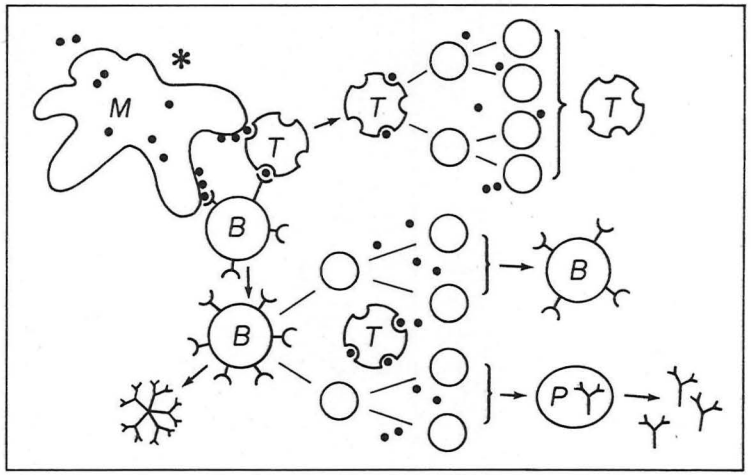
Central Processing Mechanism

For purposes of this discussion let us assume that the antigen in question is a T dependent antigen, i.e. in order for it to elicit an antibody response it must be recognized by a thymus-derived antigen reactive cell: a T lymphocyte. In an appropriate microinductive environment, a T cell is triggered by specific antigen to undergo blast transformation and division. A portion of the cellular progeny of this mitotically active cell gradually resume the morphologic features of small lymphocytes and recirculate throughout the host to act as memory cells and as effectors of delayed hypersensitivity reactions. Another portion of the population of antigen triggered cells enters into a collaborative interaction with a different lymphocyte population also capable of recognizing the same antigen: B or bursal-influenced cells whose membrane recognition structures are in fact immunoglobulin molecules with binding sites specific for the antigen. B lymphocytes confronted with antigen presented by a macrophage in the absence of a T lymphocyte are able to proliferate modestly and to differentiate into cells capable of synthesizing and secreting 19S IGM antibodies;

Figure 2



IMMUNOLOGIC REFLEX ARC



CENTRAL PROCESSING MECHANISM

"helper" T cells are required, however, to ensure that these same IgM secreting B cells can differentiate further into cells that synthesize and secrete 7S IgG antibodies, cells which ultimately assume the configuration of typical plasma cells. Thus the central processing mechanism of the immunologic reflex arc is considered to be at completion when cellular division and differentiation in response to antigen have reached that point where IgG antibody molecules are produced and antigen reactive T lymphocytes are generated to circulate in the periphery. The requirements for the effective completion of this phase of the reflex arc include antigen, macrophages, specific T and B antigen reactive lymphocytes, and a microinductive environment that can support and sustain the complex cellular and molecular events taking place. In man, these sites include the spleen, lymph nodes, Peyer's patches and other gut associated lymphoid structures such as appendix, tonsils.

The Efferent Limb

Having reached this differentiated stage in response to antigen, the reflex arc is completed through the efferent limb in which the specific effector modalities just described can freely circulate throughout the host. The interaction of these effectors with antigen in non-lymphoid tissues leads to the inactivation, destruction and/or masking of the antigen. In general, the engagement of antigen with antibody or of antigen with specifically sensitized effector lymphocyte is rarely perceived at the clinical level; instead an acute inflammatory response is usually generated and this is what catches the attention of the clinician and observer. Thus, expression of an intact immunologic reflex arc requires the enlistment of non-immunologic modes of host response. These include a variety of blood borne cells that contribute to developing inflammatory reactions - polymorphonuclear neutrophils, eosinophils and basophils, mononuclear cells of bone marrow origins (monocytes, macrophages), platelets. In addition, the molecular components of the complement, coagulation and clot-lysis systems, and small molecular weight agents with potent pharmacologic activities - histamine, serotonin, bradykinin, slow-reactive substance, etc. are also involved. The requirements therefore for a successful effectuation of a mature immunologic response comprise more than antigen and specific antibody and/or effector lymphocytes.

Because we can only measure that which manifests itself clinically, it is obvious that whatever the pathogenesis of immunodeficiency that befalls an adult, it can only be realized at the clinical level as reduced effector responsiveness. This crude finding alone does not reveal the site at which the reflex arc is disrupted nor does it give any insight into the pathogenesis of the defect.

GENERAL PATHOGENIC MECHANISMS IN IMMUNODEFICIENCY IN THE ADULT

There are several absolute requirements without which a mature immunologic response simply can not develop. The immunodeficiency disorders of infants and children have amply demonstrated that defective stem cell proliferation (presumably a failure in the hematopoietic bone marrow, of which, Swiss type agammaglobulinemia is a prototype (9); failure of thymic development and influence (leading to a relative to absolute deficiency of T lymphocytes as in the DiGeorge syndrome (10); failure of development and influence of the bursal equivalent (11,12) resulting in markedly reduced antibody production, exemplified by the Bruton type agam maglobulinemia; and malfunctioning macrophage/reticulum cells (which can not effectively carry out antigen processing or support antigen-induced proliferation and differentiation, perhaps as in the Wiskott-Aldrich syndrome (13). Thus, deficiencies of T or B lymphocytes, malfunctioning macrophages, and an aberrant inductive microenvironment are individually sufficient to prevent the development of an immune response.

In the adult, it can reasonably be assumed that these requirements were met developmentally during fetal life and childhood. Consequently, when a deficiency of immunocompetence is found in an adult individual, it can safely be expected that the cause is not developmental. This realization does not make the task of the adult patient's physician any easier. Instead, the causes of immunodeficiency in the adult appear to be legion. With the aid of the model of an immunologic reflex arc, it is possible to make certain generalizations about the diverse etiologies by attempting to assign specific sites of action.

Immuno-disruption falls under two main headings: specific and non-specific. (See Table 2.) In the latter category are listed factors which suppress or deflect the immune response without regard to a particular antigen. Agents which overwhelm the reticuloendothelial system, such as colloidal carbon or massive amounts of breakdown products from tissue necrosis (14), lead to reticuloendothelial blockade and an inability of macrophages to process antigen. Antigen may be prevented from reaching antigen recognition centers in lymph nodes by lymphatic blockade. The function of antigen reactive T cells can be impaired by toxins of bacterial or malignant cell origin (15,16), by sterile lymphocyte activation (17) in which mitogenic agents (such as viruses) induce a senseless proliferative response in the absence of antigen which renders the cells temporarily unresponsive to antigen, by destruction of T antigen reactive cells with anti-lymphocyte antibodies (18,19).

The central processing events of clonal proliferation and differentiation are affected by agents which interfere with T and B cell functions individually and wherein cooperative interactions are involved. Chalones which are biologically active inhibitors of mitosis released from actively dividing cells such as malignant plasma cells (20,21) may prevent clonal proliferation of B and/or T lymphocytes. Sterile activation of B lymphocytes can also occur rendering these cells insensitive to the inductive influences of antigen and appropriate T cells. It is now recognized that there are sub-populations of normal T lymphocytes (22) (suppressor T cells) which have the capacity under physiologic conditions of suppressing B cell activity (resulting in reduced secretion of antibody) as well as suppressing T lymphocyte effector function (23) (leading to reduced cell mediated immunity). The best evidence suggests that this is a non-specific suppression in that cells of divergent antigen recognizing ability are involved. Less well documented, but undoubtedly of important effect, is the impairment of the central processing machinery by the disruption of the inductive microenvironment caused by the infiltration of lymph nodes and spleen with malignant cells, debris laden histiocytes, and sequestered erythrocytes. The extent of the impairment covers prevention of macrophages from playing their supportive role in lymphocyte response to antigen, to interference with T-B collaborations by the random increase in non-reactive or null lymphocytes.

The efferent limb of the reflex arc can be impaired non-specifically when the rate at which immunoglobulins are catabolized is increased and when immunoglobulins and/or lymphocytes are destroyed or lost from the body at an exaggerated rate. Moreover, anti-lymphocyte antibodies can destroy effector lymphocytes almost as well as antigen reactive cells. "Toxins" of whatever origin can also impair effector cell function. To the extent that display of the efferent limb of the reflex arc depends upon non-specific mediators such as complement, neutrophilic granulocytes, etc., loss or malfunction of these modalities will also present as an efferent limb deficiency.

While all of these inhibitors of the mature development of the immune response to antigen are immunologically non-specific, it is worth pointing out that impairment may be restricted in terms of antigen. For that matter, one popular theory accounting for tolerance of self maintains that the absence of auto-immune destruction under physiologic circumstances, represents an immunologically specific impairment of immune responsiveness probably achieved through the positive ability of self antigens to

Table 2.

INTERRUPTION OF IMMUNOLOGIC REFLEX ARC
BY SPECIFIC AND NON-SPECIFIC MECHANISMS

	AFFERENT LIMB	CENTRAL PROCESSING	EFFERENT LIMB
SPECIFIC	Antigen: Antibody Complexes (ARC)	IgG Antibody (IgM AFCs)	Antibody (Effector T Cells)
	Antigen-Low Dose, IV (ARC without Mϕ)	Antigen-Low Dose, IV (ARC without Mϕ)	Antigen-High Dose (Antibody)
NON-SPECIFIC	Antilymphocyte Serum (T-ARCs)	Suppressor T Cells (B & T ARCs)	Antilymphocyte Serum (Effector T cells)
	Sterile Activation (T-ARCs)	Sterile Activation (B & T ARCs)	Hypercatabolic Rate (Antibody)
	Reticuloendothelial Blockade (Macrophage)	"X" Cells-tumor, Mϕ, etc. (T-B Interactions)	External Loss (Antibody and Lymphocytes)
	Lymphatic vessel Blockade (ARC and Mϕ)	Chalones (B & T Cells)	"Toxins"
	"Toxins"	"Toxins"	

Items in parentheses are principal sites of action of mechanism listed.

Mϕ = Microphage
AFC = Antibody Forming Cell
ARC = Antigen Reactive Cell

disrupt the reflex arc (24). There are several mechanisms which can be incriminated in the impairment that can be obtained for specific antigens. For example, refering once again to Table 2, the afferent limb can be blocked specifically by antigen which reaches the antigen reactive cell before macrophage processing, an event that renders the antigen reactive cell inactive (25). In addition, antigen-antibody complexes are able to interact directly with antigen reactive T lymphocytes and prevent subsequent interactions with B lymphocytes or antigen alone (26). In both instances, effective recognition, the crucial first step in immune responsiveness, can be aborted.

In a manner similar to its action in the afferent limb, antigen that reaches antigen-reactive B cells in low concentration and perhaps without an intervening macrophage is able to inactivate specifically the clone of cells that would normally have expanded and differentiated into specific antibody forming cells. Normally, there is a feedback control mechanism by which IgG antibody is able to inhibit the further secretion of IgM antibody of identical specificity (26). It is not unlikely that under pathologic circumstances IgG antibody could accomplish this interruption of B cell activity prematurely and thus reduce the total amount and duration of specific antibody synthesis. Less clearly understood is the role of anti-idiotypic antibodies (27). These antibodies, which are directed at the unique molecular configuration of the antibody-combining site on other antibody molecules, appear to be able to disarm and inactivate B and T antigen reactive cells via the antigen receptor site on the plasma membrane and could in this manner turn off the developing immune response (28). The role of these anti-antibodies in the normal immunologic response as well as in pathologic situations remains to be worked out.

Specific impairment of the efferent limb of the reflex arc can be obtained by excess antigen which would inactivate specific antibody (25). In addition, when antibody and effector T lymphocytes are directed at the same antigenic determinants, the former is capable of interfering with the function of the latter and may eventually protect the antigen, rather than leading to its inactivation or destruction. Experimental examples of this phenomenon in tumor immunity known as enhancement (29) are common.

LABORATORY DIAGNOSIS OF IMMUNODEFICIENCY

The suspicion that immunodeficiency exists in an adult generally comes from an awareness that this disorder is associated with certain clinical settings. But in contemporary medicine, documentation of immunodeficiency depends heavily upon laboratory assistance in describing the extent and identifying the characteristics of the deficiency. Tests of immunocompetence can conveniently be divided into those that assay cell mediated immunity, and those that measure antibody-mediated immunity. In addition, there are diagnostic tests which document the presence of abnormality among the immunologically non-specific effector mechanisms. Some tests are purely descriptive and tell something about the previous immunologic experience of the patient while others are provocative and indicate the functional capacity of the patient's immune system at the time of testing. Finally, some procedures are simple to perform and relatively inexpensive and therefore become useful screening tests of immune function; other tests which are more complex, difficult and expensive are reserved for definitive work-up and description of the particular immunologic lesion.

Screening Evaluation

In Table 3, screening tests of immune function are listed. With the aid of these relatively simple tests, it should be possible to determine whether the patient is making normal quantities of the three major immunoglobulins found in the serum, whether

Table 3.

LABORATORY TESTS OF IMMUNOLOGIC COMPETENCE

SCREENING TESTS

ANTIBODY	CELL-MEDIATED	NON-SPECIFIC
Serum Protein Electrophoresis	Absolute Lymphocyte Count In PB	Absolute Granulocyte Count
Immunoelectrophoresis	Intradermal Skin Tests with	Serum Third Complement Component
Isohemagglutinins	P.P.D, Mumps, Candida,	C. reactive protein
	Trichophyton, SK/SD,	E.S.R.
Febrile Agglutinins	Histoplasmin	
Heterophile Antibodies		
ASO Titer		

common antigens in the environment have elicited typical antibody responses, whether delayed hypersensitivity is intact to antigens commonly experienced, and whether the capacity to mount an inflammatory response is grossly intact. Signals to continue the immunodeficiency work-up further include: (a) positive Schick test in an individual with previous history of Diphtheria toxoid immunization; (b) negative isohemagglutinins except in patients who are of AB blood type; (c) negative responses to all skin test antigens; (d) lymphocyte count of less than 1000; (e) deficiency of one or more of the immunoglobulins in serum; (f) granulocyte count of less than 1500 . Lymphocyte counts and granulocyte counts in excess of 10,000 would naturally be evaluated as part of the hematologic work-up of unexplained leukocytosis.

Definitive Evaluation

The definitive work-up of suspected immunodeficiency is drawn from the laboratory procedures listed on Table 4. The descriptive tests allow an assessment of the current status of immune effectors in the unprovoked host. Positive intradermal and scratch tests for reagin type allergy are indications that immunocompetence probably exists. Negative responses do not necessarily imply that immunodeficiency is the cause. On the other hand, characterization of B cells in the peripheral blood does give useful information in that regard. Approximately 30% of circulating lymphocytes should express surface immunoglobulins or complement receptors as evidence that they are, or can differentiate into, antibody forming cells (30). An independent assessment of the patient's B cell compartment can be gained by histologic evaluation of a lymph node: the presence of follicular concentrations of cells in the cortex and germinal centers indicates that the bursal influenced aspect of mature immunologic responsiveness is morphologically intact (31).

The proportion of circulating small lymphocytes that form spontaneous rosettes with sheep RBCs is one measure of the patient's load of thymus influenced cells, the normal value being 60-70% rosette forming cells (32). T cells can also be identified by a specific anti T cell antibody reagent. Another means of determining T cell function is to culture peripheral blood leukocytes with PHA, Concanavalin A (T cell mitogens) and with allogeneic leukocytes (33,34). More sophisticated measures of T lymphocyte function include the elaboration of blastogenic factor (35) and lymphotoxin (36) after exposure to a mitogen. In addition, lymph node biopsy can reveal whether the so-called thymus-dependent areas are preserved: especially the deep cortical layers of lymphocytes which contain the highly specialized post-capillary venules (31).

Determination of Factor B levels in the serum reflect the extent to which the patient's alternate pathway of complement activation can be brought into play in the mounting of an inflammatory response. Tests of granulocyte function: phagocytosis, migration under a chemotactic stimulus, etc. bear importantly on the ability of this first line of non-specific defense to deal with invading pathogens.

As part of the definite work-up of immunodeficiency in adults , it is imperative that functional tests be made of the patient's ability to respond and these tests are listed in Table 4 under the heading of Provocative Tests. For humoral immunity, patients can be immunized with polyvalent influenza vaccine and with Salmonella Typhosa vaccine and their subsequent serum antibody response compared with that in normal individuals. Patients with intact immunologic reflex arcs will respond briskly to the conventional immunization procedures; on rechallenge they will exhibit an anamnestic response. Application of dinitrochlorobenzene to the skin provides a means of assessing cell-mediated immunity. Virtually 100% of normal individuals either exhibit a recrudescence of local inflammation at the site of application 2 weeks later, or respond with an inflammed, erythematous reaction to a non-toxic subsequent application of the same material. In a similar kind of test, allografts of skin can be placed on a patient suspected of cellular immunodeficiency. In a genetically un-

Table 4

LABORATORY TESTS OF IMMUNOLOGIC COMPETENCE

DEFINITIVE TESTS

	ANTIBODY	CELL-MEDIATED	NON-SPECIFIC
DESCRIPTIVE	Quantitative Serum Igs	Leukocyte Cultures: Mitogenic response to PHA, Con A, Allogeneic Leukocytes	Granulocyte Functional Tests: NBT, Bactericidal activity, Chemotaxis
	Schick Test	T Cell Identification in peripheral blood by Sheep RBC rosette formation and anti-T cell antibody	Serum Factor B
	Reagin Skin Tests		Bone Marrow Examination
	B Cell Identification in peripheral blood by Ig, Fc, and C3 receptors	In Vitro elaboration of lymphokines by activated peripheral blood cells	
	Lymph Node Biopsy for Histology	Lymph Node Biopsy for Histology	
PROVOCATIVE	Primary Immunization with Polyvalent Influenza vaccine	Primary Sensitization of skin with DNCB	Rebuck Skin Window
	Salphonella Typhosa O vaccine	Orthotopic graft of allogeneic skin	Croton Oil Patch Test
	Secondary Immunization with Diphtheria-Tetanus vaccine		

related population, allogeneic skin grafts are rejected typically before 12 and almost always before 15 days. Grafts that survive beyond that interval reveal an underlying cellular defect in immunity. The Rebuck skin window (38) affords one useful way of assaying the ability to mount a non-immunologic cellular response to an inflammatory stimulus.

There are additional tests of immunologic competence that can be carried out for highly specialized circumstances. Where appropriate, these will be mentioned during the next section which deals with the spectrum of immunodeficiency seen clinically in adults.

CLINICAL SPECTRUM OF IMMUNODEFICIENCY IN THE ADULT

Immunodeficiency in adults presents in extraordinarily diverse ways. In fact, it is possible that our contemporary view of what constitutes immune deficiency is too restricted and may ultimately come to include syndromes and disorders now not even suspected of being in this category. Even within the past 10 years, the number of diseases which are thought to result from immune deficiency is larger by an order of magnitude than was previously believed.

The possibility of immune deficiency may surface only when it is inadvertently discovered that a patient has abnormally low serum levels of one or more of the known serum immunoglobulins, or when the circulating lymphocyte count is markedly reduced. More commonly, immunodeficiency becomes a consideration in a patient whose recent medical history includes a great number of local or systemic infections which may be bacterial, viral or fungal, in cause. A survey of various infecting organisms is listed in Table 5 (37) for 2 reasons: first, to give a view of the spectrum of organisms that are known to cause serious infections in patients with immunodeficiency, and second, to indicate that the type of organism can give a clue as to the probable nature of the immunologic defect. It would appear that protection against infections by organisms such as the staphylococcus and Serratia marcescens is provided more by the non-specific modality of host reactivity than by any specific immunologic response. Alternatively, the Pneumococcus and Pseudomonas bacteria prove difficult to handle by patients whose humoral immune response is defective, while many viral and fungal infections signal a cellular immune deficiency.

Because of the impact on medical thinking of the revolutionary idea of immunologic surveillance by which the immune apparatus is supposed to keep us clean and pure of malignant cells, the mere appearance of malignancy in a patient may raise the spectre of an underlying immunodeficiency. To be sure, in the patient with advanced malignant disease, immunodeficiency is a common finding. (39). Less well known is the fact that many of the so-called auto-immune disorders, in which exaggerated immune responses to self components are found, are also expressions of immunodeficiency, especially with regard to exogenous pathogens, and this deficiency may be a clinically important aspect of the disease (40).

At least for the last two categories mentioned - malignancy and auto-immune disease - equally valid arguments can be advanced which state that immunodeficiency precedes the development of, or alternatively is the consequence of, the clinical appearance of both conditions. This raises a general problem in classifying immunodeficiency in the adult: is it cause or is it effect? It is common practice to classify a multifaceted syndrome into primary and secondary forms in which the former is thought to arise de novo while the latter is the consequence of a preceding or attendant disease. Although it is possible to categorize immune deficiency disorders by other criteria, in this presentation immune deficiency in the adult will be considered according to whether the defect is thought to be primary, or secondary to some other process, usually a disorder that is non-immunologic.

Table 5

CONSTELLATIONS OF INFECTION IN IMMUNODEFICIENCY DISORDERS

	HUMORAL DEFECTS	CELLULAR DEFECTS	NON-SPECIFIC DEFECTS
PATHOGENS	Pneumococcus	Rubeola	Staphylococcus
	Haemophilus influenzae	Varicella	Klebsiella sp.
	Streptococcus	Vaccinia	Aerobacter aerogenes
	Meningococcus sp.	Cytomegalic inclusion disease virus	Serratia marcescens
	Pseudomonas aeruginosa	Mycobacterium tuberculosis	Candida albicans
	Hepatitis virus	Histoplasma	Aspergillus
	Pneumocystis carinii		Nocardia

PRIMARY IMMUNODEFICIENCY IN THE ADULT

It has already been pointed out that the primary immune deficiency disorders have been categorized and described for the Pediatric population and virtually every review of immunodeficiency now in the literature is heavily committed to the syndromes resulting from developmental defects. Because these disorders are a topic in and of themselves, and because they are rarely seen by the clinician who deals with adult patients, the developmental and genetic causes of immunodeficiency will not be considered here in any detail. Instead, a list of these disorders taken from Bellanti's Textbook on Immunology is presented in Table 6 (7) and is provided so that the few disorders that are seen with reasonable frequency in the adult population can be singled out (note asterisks). For this discussion, the assumption has been made that if immunodeficiency has appeared in a post-pubescent individual, it has developed on a background of a previously intact and mature immunologic apparatus.

In Table 7, the Primary immunodeficiency disorders in adults are listed. Now that serum protein electrophoresis and immunoelectrophoresis have become common laboratory procedures, a large proportion of the patient population has been screened and a good deal is known about the immunoglobulin deficiency states in adults.

Probably the most common single disorder in this category is the isolated IgA deficiency (Type III, Dysgammaglobulinemia). This abnormality is found with a frequency of approximately 1/500 adults (41) and has given rise to much speculation on the meaning and significance of IgA, the predominate immunoglobulin found in bodily and external secretions. Not only are these patients deficient in serum IgA, but their tears, saliva, etc. also lack this class of immunoglobulins. It was no surprise that the first reports of this disorder came from cases with a high frequency of upper respiratory and sinus infections. As more individuals were screened, increasingly large numbers of apparently normal persons with isolated IgA deficiency were reported. At this point, no simple, single, clinical syndrome is tightly associated with this abnormality. One intriguing observation that has emerged from studying this group of patients is that auto-immune disorders occur with a high frequency: Lupus, rheumatoid arthritis, auto-immune hemolytic anemia. The mechanism of this curious relationship is totally unclear, but the association brings into focus the tendency of immunodeficiency and auto-immunity to go hand in hand.

Type I and Type II Dysgammaglobulinemias, which also exhibit reduced serum IgA, variably express abnormally low levels of IgG and/or IgM. Type II has a peculiar association with the syndrome of gastro-intestinal malabsorption and nodular lymphoid hyperplasia of the lamina propria of the intestine. Rarely, cases of diffuse deficiency of IgG, A and M are seen in adults, reminiscent of the childhood syndrome of Bruton's type agammaglobulinemia (42). Reduced numbers or even absent B lymphocytes in the peripheral blood of these patients suggests that they have acquired a defect in the ability to generate cells required for Ig synthesis.

More recently, Waldmann has championed a form of immunodeficiency in adults which he has termed Common Variable Immunodeficiency (43). This embracing term may ultimately replace the designation of Dysgammaglobulinemias for the syndromes just described. Common Variable Immunodeficiency takes into account the fact that immunoglobulin deficiencies in the serum occur in various patterns without signifying any particularly unique clinical picture. In addition, there may or may not be an associated deficiency in cell-mediated immunity. What provides validity to this notion and sets it apart from the agammaglobulinemias of children is the demonstration that adult patients with common variable immunodeficiency have

Table 6

DISORDERS OF SPECIFIC IMMUNITY - PRIMARY IMMUNODEFICIENCY

HUMORAL DEFECTS

Agammaglobulinemia
- Congenital agammaglobulinemia
- Acquired agammaglobulinemia*
- Physiologic agammaglobulinemia
- "Pseudohypogammaglobulinemia"

Dysgammaglobulinemia
- Type I - low A and G, high M*
- Type II - low A and M, normal G*
- Type III - low A, normal G and M*
- Type IV - low G, normal A and M
- Type V - low M, normal G and A
- Type VI - normal G, A, and M
- Type VII- low G, high A, normal M

DEFECTS OF CELL-MEDIATED IMMUNITY

With Thymic Defects
- Nezelof Syndrome
- DiGeorge Syndrome

Without Thymic Defects*

COMBINED DEFECTS

Wiscott-Aldrich Syndrome
Ataxia telangiectasia
Swiss Type Agammaglobulinemia

*Disorders seen in adults

Table 7

PRIMARY IMMUNODEFICIENCY IN THE ADULT

HUMORAL DEFECTS

- Acquired Agammaglobulinemia with deficiency of B lymphocytes
- Type I Dysgammaglobulinemia - low A and G, high M
- Type II Dysgammaglobulinemia - low A and M, normal G
- Type III Dysgammaglobulinemia - low A, normal G and M
- Common Variable Immunodeficiency with normal levels of B lymphocytes*
- Isolated IgE Deficiency

CELLULAR DEFECTS

- Mucocutaneous Candidiasis
- (Malignancy)
- (Auto Immune Disorders, Generalized)*
- Aging*

*May exist as a combined cell-mediated and humoral deficiency

essentially normal circulating levels of B lymphocytes (44)! That is - lymphocytes with Immunoglobulins on their surface which fulfill other criteria for having come under the influence of the mammalian bursal-equivalent are present within the blood. On lymph node biopsy, the nodal architecture is intact, exhibiting normal follicular development. Thus, although the cellular machinery for making immunoglobulins in response to antigenic challenge is present, these patients fail to respond by making significant amounts of antibody. Within the past few months this curious paradox has become even more intriguing. Waldmann et al (45) have demonstrated that in these patients T lymphocytes are circulating in the peripheral blood which have the capacity of turning off immunoglobulin synthesizing B cells. It is suggested that this situation is analogous to the experimental observation in laboratory rodents that suppressor T cells can inhibit antibody production by appropriately stimulated B cells (22). If this observation in humans is confirmed, it will add a new dimension to our thinking about mechanisms of immunodeficiency in the adult. A very recent communication has suggested that a deficiency of suppressor T cells may be the cause of chronic active hepatitis of viral origin (46), while another postulates T cell dysfunction in lipoid nephrosis (47).

IgE, the immunoglobulin associated with atopic and allergic states, and generally held responsible for the clinical features of hay fever and hives, is present normally in the serum in vanishingly small quantities. In fact, very few laboratories are equipped to measure IgE levels quantitatively; consequently, much less is known about the clinical spectrum of IgE deficiency (48,49). As in IgA deficiency, the first reports of patients with absent serum IgE described severe recurrent respiratory infections and it was thought perhaps that this immunoglobulin along with IgA was important in local immune defense of the respiratory tract and gut. A sufficient number of subsequent reports have modified that view and it is known that IgE deficiency is not necessarily associated with any particular clinical syndrome. Moreover, it is usually present in the serum even in the face of deficiencies of the other Ig types. It is not understood why deficiencies of IgG,A and M should not also include IgE, but this realization carries certain far-reaching implications about the inductive process of immunity and whether a true B stem cell exists from which the various Ig synthesizing types differentiate.

The concept of Common Variable Immunodeficiency includes the variable expression of deficiency of cellular immunity. There are occasional patients with primary defects of only the cell-mediated limb of the immune response. These are generally grouped under the heading of Mucutaneous Candidiasis since these patients almost invariably suffer from chronic and severe cutaneous infections with Candida Albicans (50). While some of these individuals are deficient in the number of T lymphocytes (51), more commonly the defect is a functional one (52) in which the patient's cells are unable to secrete one or another of the phenomenologically defined mediators or lymphokines such as mitogenic factor, macrophage migration inhibition factor, lymphocytotoxin, etc. This group of patients is obviously comprised of a heterogeneity of pathogenic mechanisms and the clinical syndrome may very well include patients with deficient macrophage function, but normal T cell function.

Before leaving this consideration of the primary immunodeficiency disorders of the adult, it is reasonable to mention the immunodeficiency which seems to be a normal accompaniment of aging. Whether studied in aging laboratory animals or in human beings, (3,37) it is generally agreed that through time the thymic dependent component of the immune response begins to fade. This expresses itself as reduced responsiveness to various skin tests which normally induce a delayed hypersensitivity reaction. Alternatively, the production of serum antibodies and immunoglobulins appears to increase with advancing age. Since the synthesis and secretion of IgG antibody requires the assistance of thymic derived cells, this aspect of thymic

function seems preserved in the elderly. Waldmann's demonstration that there are suppressor T cells functioning in man may offer an alternate hypothesis for increased immunoglobulin production in the aged: the gradual loss of suppressor T cell activity would release more and more B cells to synthesize their product upon antigenic stimulation. It is even possible that the increased incidence of auto-antibodies in the elderly reflects a similar pathogenesis. This immunologically "hot" area will be providing increased grist for the clinical mill over the next several years.

SECONDARY IMMUNODEFICIENCY IN THE ADULT

By far the most common form of immunodeficiency in adult patients is that which is secondary to some underlying disorder. The secondary deficiencies lend themselves to a cellular-based classification similar to the primary deficiencies with the exception that another major category is required, immunologically non-specific disorders. Clinical common sense states that this is the most common form of deficiency of all. In Table 8, the Secondary Immunodeficiency Disorders are listed under the headings: Immunologically Non-Specific, Humoral Defects, Cellular Defects, Combined Defects.

Non-Specific Deficiencies

In the immunologically non-specific category, tests of immunologic competence, at least by conventional means, generally reveal an intact apparatus and response. In these patients, the first line of bodily defense, which most assuredly is not immunologic, is compromised. The list of diseases is an eclectic rather than an exhaustive one, the examples being chosen because of the instructive modes by which the host's non-specific defense mechanisms are compromised. In patients with leukemia and aplastic anemia, functionless or absent granulocytes rob the patient of his ability to phagocytize organisms that are normally inactivated in this manner. In patients with burns the integumental wrapper is destroyed and pathogens have easy access to the vulnerable tissues beneath. In diabetes mellitus, while one can document under experimental conditions evidence of lymphocyte dysfunction, it is undoubtedly the insulin dependent dysfunction of granulocytes and macrophages, along with the enhanced ability of bodily fluids rich in glucose to act as culture media that are the major determinants of repeated infections.

The hemoglobinopathies share with the splenectomized patient the loss of a major source of reticuloendothelial and phagocytic removal of pathogenic organisms from the blood. In addition, the high serum iron levels that exist in the hemoglobinopathies has recently been suggested as the pathogenic force that can tip the balance in favor of microbial organisms whose continued success depends upon a ready source of free iron (53).

Disorders of lymph and venous flow, whether found in congestive heart failure, nephrotic syndrome, or idiopathic lymphedema render the patient more susceptible to the development of local infections.

Specific Immunodeficiency

The deficiencies of specific immune responsiveness are categorized in Table 8 according to whether the defect is thought to be predominately humoral, cellular, or combined. And while this categorization is useful, it also seems appropriate to view these deficiencies from the standpoint of aberrations of the immunologic reflex arc.

Table 8

SECONDARY IMMUNODEFICIENCY DISORDERS IN THE ADULT

HUMORAL DEFECTS	CELLULAR DEFECTS	COMBINED DEFECTS	NON-SPECIFIC DEFECTS
Post-Splenectomy	Sarcoidosis	Severe Malnutrition	Acute Leukemia
Protein Losing Enteropathy*	Hodgkin's Disease	Uremia	Aplastic Anemia
Plasma Cell Dyscrasias* (Malignant)	Systemic Lupus Erythematosis	Severe Burns	Diabetes Mellitus
Lymphomas and Lymphosarcomas*	Acute Viral Infections (Measles, Herpes)	Intestinal Lymphangiectasias	Congestive Heart Failure
Nephrotic Syndrome	Advanced Malignancies		Cystic Fibrosis
Myotonic Dystrophy	Chronic Granulocytic Leukemia with Splenomegaly	(Drug-Induced)	Hemaglobinopathies
Malnutrition	Advanced Systemic Infections		Complement Deficiencies
Exfoliative Dermatitis	Aging		Post-Splenectomy
(Cyclophosphamide)	(Steroids)		

*When severe, cellular defects may also occur.

It is the contention of this presentation that considering immune deficiency in this manner in adults assists in understanding the pathogenic mechanisms that are operative. Table 9 consists of a list of the secondary immunodeficiencies in which an attempt has been made, based on the most compelling evidence available, to indicate where the site of the defect resides.

Humoral Defects

Immunologically specific deficiency may present predominately as a reduction in immunoglobulins and antibody production. When considering immunoglobulin serum levels as markers of deficiency, it must be kept in mind that the maintenance of a normal serum level reflects not only the individual's capacity to synthesize and secrete these proteins, but their catabolic rate. The normal T $\frac{1}{2}$ for IgG is approximately 21 days. Normal decay curves can be established for the other immunoglobulins and reflects the fact that there is a normal turnover of these proteins. While some are normally lost through external body secretions, the majority are enzymatically degraded primarily within the reticuloendothelial system. Not unexpectedly, therefore, one category of Ig deficiency disorders results from an accelerated loss or destruction of immunoglobulins. Excessive loss of Ig molecules is seen in the protein losing enteropathies (54), in the nephrotic syndrome (55), and in exfoliative dermatitides and burns (56). Excessive destruction of Ig molecules, of which the best information concerns IgG, occurs following splenectomy (57), and curiously, in the genetic disorder, Myotonic Dystrophy (58). In all of these conditions, studies of the afferent and central processing components of the immunologic reflex reveal that they are intact. And although the effector molecules are produced in normal or perhaps even increased quantities, their excessive loss and/or destruction impairs the expression of immunity and as a consequence, infections, chiefly involving encapsulated bacteria, are a hazard.

There are, however, disorders in which the finding of various Ig serum deficiencies reflects a marked impairment in synthesis due to an associated disorder. Early in starvation and malnutrition there is a relatively selective depression of B lymphocyte function (59); a similar depression can be achieved with cyclophosphamide in appropriate dosage range (60). Reduced levels of Ig in serum are associated with most of the lymphomatous malignancies (61), and is almost a regular finding in patients with plasma cell dyscrasias (62). It should be pointed out that in this last group of patients, there is good evidence that accelerated destruction of immunoglobulins occurs as well, so that the reduced serum Ig levels (with the exception of the M spike) result not only from reduced synthesis, but increased destruction. In malnutrition, lymphomas and plasma cell dyscrasias, attempts at specific immunization to new antigens are relatively or absolutely unsuccessful indicating that the reflex arc is disrupted. Since antigen recognition by T lymphocytes is preserved until very late in the course of these diseases, it is surmised that the disruption occurs at the level of central processing of antigen. Several mechanisms suggest themselves: reduction in the numbers of antigen-sensitive B cells which can ultimately differentiate into antibody-forming cells; suppression of B cell function by factors released from malignant cells (chalones have been implicated in plasma cell dyscrasias)(20); interference with T-B cellular interactions by the interjection of antigen-irrelevant tumor cells (63). These are but a few of the more plausible ideas: no single mechanism can be brought forward as the most likely candidate. It is of some interest that patients with previous history of allergic disorders such as hay fever and asthma will experience a remission upon the onset of malignant lymphoma (64), a clear indication that the immunodeficiency is acquired and extends to immunological memory as well as primary sensitizability. It should be pointed out that as the malignant disorders proceed to their final stages, the Ig deficiency is compounded by the development of cell-mediated immune deficiency as well.

Cellular Defects

Cell-mediated immune deficiency with preserved humoral immunity can arise secondary to an underlying disorder. Anergy, i.e. the inability to display delayed hypersensitivity to cutaneous challenge with a battery of appropriate antigens, has been described in sarcoidosis, Hodgkin's disease, and in advanced infections with tubercle bacilli, coccidiomycosis, and leprosy (65). In sarcoidosis, the defect has been shown not to be an inherent property of the patient's skin, but to be related to an aberration of leukocyte function (66). Since these patients are able to reject skin allografts with relatively normal vigor, not all aspects of cell-mediated immunity are depressed. In vitro studies of sarcoid lymphocytes reveal an impairment in their ability to be turned into mitotic activity by mitogens (67). A recent report reveals that the circulating level of responding T cell is also reduced in these patients (68). Thus, to some extent, lymphopenia may be responsible for the reduced cell-mediated response, but in addition, it is clear that sarcoid T cells are functionally aberrant, unable to accomplish the appropriate mitogenic response to an inductive stimulus, the first step in the generation of a mature immune response. Anergy of a similar clinical expression exists in Hodgkin's disease, but unlike in Sarcoidosis, these patients display an increased susceptibility to infections with tubercle bacilli, various fungi, and viruses (65). The recent classification of Hodgkin's disease according to histologic type (69) has brought into line and made some sense out of the relationship between anergy and this disease. As the disease proceeds from lymphocyte predominant to lymphocyte depleted, the presence and severity of cellular immune deficiency increases. The lymphopenia of moderately advanced Hodgkins is primarily due to a lack of T lymphocytes. Thus it is no surprise that expressions of the activities of these cells as effectors of delayed hypersensitivity are reduced. However, simple deficiency of T lymphocytes can not explain totally the anergy of these patients for in addition, attempts to transfer delayed hypersensitivity to these patients with specifically sensitized allogeneic cells have been almost routinely unsuccessful. Moreover, the imapired response in vitro of Hodgkins lymphocytes to PHA is at least partly dependent upon an unknown factor in their plasma (70); plasma from patients who are anergic when mixed with lymphocytes from normal individuals suppresses the in vitro response of those cells to PHA and other mitogens. Just to complicate matters, there have been reports that the ability of these patients to undertake a primary immunization with production of antibody may also be impaired (71). This is an inconsistent finding and may be related to advanced stage of the disease at the time of testing. Thus the patient with Hodgkin's disease has his immunologic reflex arc interrupted at the afferent limb (reduced numbers of antigen recognizing cells), the central processing mechanism (unable to clonally expand and perhaps differentiate when stimulated with antigen), and the efferent limb (a plasma factor which interferes with effector cell function).

Patients that are severely infected with Tubercle bacilli may display anergy to P.P.D. during an interval when their ability to respond to other test antigens is intact. This selective anergy (which becomes widespread when the disease overwhelms the host) expresses itself in failure of skin test reactivity to P.P.D and in the failure of the patient's cells to respond to P.P.D. in culture. This restricted type of antigen specific cell-mediated deficiency may bear some resemblance to that which exists or is postulated to exist early on in the course of a developing malignant neoplasms. In this case, the host is suspected of being specifically unable to recognize the neo-antigens of the tumor in a manner that will lead to its successful destruction by effector lymphocytes (72). Generally, however, evidence of fading cellular immune function in malignant disease occurs late in the course of the disease and is non-specific, in the sense that the anergy exists not only for tumor specific antigens, but for unrelated antigens as well (73). The relationship between immunocompetence and malignancy is a complex and unresolved one with arguments favoring which develops first being equally unreasonable on both sides. Operationally, the

characterization of immunocompetence in a patient with a malignant neoplasm has proved worth while as a means of predicting the course of the tumor in that patient. Increasing evidence of immunodeficiency at the time of initial diagnosis of cancer implies an increasingly bad prognosis for the patient with his disease (74). The association suggests, but by no ways proves, a causal relation.

It may be somewhat unexpected to learn that cellular immune deficiency may accompany systemic lupus erythematosis (75). This interesting association has led to the observation that the serum of these patients contains an auto-antibody capable of destroying the patient's own lymphocytes (76). It is reasonable to speculate that this auto-antibody is responsible for the reduction in T cell function. In fact, harkening back to the postulated role for suppressor T cells, the anti-lymphocyte antibody may re-enforce its own production by simultaneously destroying T cells capable of suppressing auto-antibody production.

Transient anergy as revealed by delayed skin testing has been reported for many years in association with acute viral infections (77, 78). Most commonly, the association is made with measles, but herpes infections also possess this capability. Recent studies of leukocyte culture from virus infected individuals suggest that the pool of antigen reactive cells may be depleted (79).

If one regards aging as a primary disease rather than the natural course of accumulated insults, then the relatively selective loss of T cell function exhibited with old age might be regarded as an expression of a secondary immune deficiency. Its mechanism remains obscure.

Combined Defects

Without exaggeration, it can safely be said that in the terminal stages of practically any systemic disease, deficiency of both cell and antibody mediated immunity can occur. Thus, in severe malnutrition, burns, malignancy, etc. there may be profound dysfunction of the entire immunologic apparatus. And by that time, it is probably not the most important feature of the patient's clinical dilemma. Alternatively, there are several disorders in which immunocompetence of both effector modalities seems equally affected, and in which its recognition may benefit the patient. In certain of the protein losing enteropathies, the intestinal loss of immunoglobulins may be accompanied by significant loss of leukocytes, including lymphocytes (80). Severe lymphopenia can be induced by this means, and tests of cellular function in vivo and in vitro may be abnormal. It is rarely possible however to implicate these deficiencies in either the pathogenesis of the patient's basic disease, or in secondary infections.

Table 9

PATHOGENIC MECHANISMS OF SECONDARY IMMUNODEFICIENCY

BASED ON THE IMMUNOLOGIC REFLEX ARC

HUMORAL DEFECTS	AFFERENT LIMB	CENTRAL PROCESSING	EFFERENT LIMB
Protein Losing Enteropathy	-	-	-
Nephrotic Syndrome	-	-	+
Myotonic Dystrophy	-	-	+
Exfoliative Dermatitis	-	-	+
Burns	-	+/-	+
Post-Splenectomy	+/-	+	+
Plasma Cell Dyscrasias (Malignant)	-	+	+
Lymphoma, Lymphosarcoma	+/-	+	-
Cyclophosphamide Therapy	+/-	+	-
CELLULAR DEFECTS			
Sarcoidosis	-	-	+
Chronic Granulocytic Leukemia, Splenomegaly	-	+/-	+
Acute Viral Infections	+	+	-
Advanced Systemic Infections	+	+	-
Hodgkin's Disease	+	+/-	+
Systemic Lupus Erythematosis	+	+/-	+
Aging	+	+	+
Steroids	+	+	+
Advanced Malignancy	+?	+?	+?
COMBINED DEFECTS			
Severe Malnutrition	+	+	-
Uremia	+/-	+/-	+
Severe Burns	+/-	+	+
Intestinal Lymphangiectasias	-	-	+

SUMMARY

The elaboration of another scheme for the classification of a particular set of related human diseases is not in itself of any significance. It can only derive its worth from a rekindling of interest in a particular arena or by setting the stage for new insights into pathogenesis or therapy. The consideration of Immunodeficiency in the adult in terms of the immunologic reflex arc has been undertaken on the strength of the opinion that aberrations which occur in adults must generally result from normal processes gone awry, rather than from a failure in development. Not only does this imply that totally different pathogenic mechanisms can result in the same effector deficiency, but that the establishment of effective and appropriate therapy will only come when the proper pathogenetic mechanisms are elucidated. At the least, one might expect that the clinical approach to the adult patient with suspected immunodeficiency will be enhanced; at the most, one might hope that more effective therapeutic maneuvers can be generated for the relief of patients so afflicted.

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