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DISEASES OF IMMUNE REGULATION

During the past five years, our knowledge of the human immune response has expanded enormously. This presentation will outline several of these fascinating observations and relate them to human diseases in which deviation from normal immunity has occurred.

I. Regulation of the immune response
   - A. T-lymphocytes, B-lymphocytes and macrophages cooperate by surface membrane interactions after antigen exposure
   - B. Thymus-dependent and independent antigen stimulation
   - C. Responders vs. non-responders: The role of the histocompatibility-immune response gene complex
   - D. Three types of T-lymphocytes: Suppressors, helpers, and killers
   - E. Three types of immunological tolerance: Antigen paralysis, T-cell suppression, and high affinity IgG antibody:antigen complexes (blocking factors)
   - F. Other soluble regulators of immunity-Thymosin, allogeneic effector factor, antigen specific T-cell helper factors, lymphocyte mitogenic factor, transfer factor, C-reactive protein, α-fetoprotein

II. Mucocutaneous candidiasis
   - A. Four defects with a common clinical expression
   - B. Role of antigen-load on the host response
   - C. Common denominator between chronic infections and neoplasia: Impaired immunity related to blocking factors and saturated Fc receptors?

III. Acquired hypogammaglobulinemia (too much T-cell suppression)
   - A. The chicken model of "infectious" agammaglobulinemia
   - B. The role of suppressor T-cell function in common variable hypogammaglobulinemia in man

IV. Normal pregnancy, neoplasia and ataxiatelangiectasia
   - A. Physiological variation and function of serum α-fetoprotein
   - B. Hepatoma and other forms of neoplasia related to suppressed T-cell function in the presence of elevated serum α-fetoprotein
   - C. All patients with ataxiatelangiectasia show elevated serum levels of α-fetoprotein

V. Lymphoproliferative disorders
   - A. Sjögren's syndrome, pseudolymphoma and lymphoma
   - B. Sèzary syndrome vs. chronic lymphatic leukemia
   - C. Suppression of normal immunoglobulin (but not myeloma Ig) synthesis in multiple myeloma

VI. Systemic lupus erythematosus (too little T-cell suppression?)
   - A. Are patients with SLE under-responders or over-responders to foreign antigens?
   - B. Evidence for loss of T-cell suppression in the NZB/W mouse model of SLE
   - C. The argument for Ir gene defects in patients with SLE

VII. Auto-antibodies can enhance other forms of immune abnormality
   - A. Lymphocytotoxic antibodies in viral diseases and SLE
   - B. Atopic diseases: What role does IgM-anti-IgE play?
   - C. Some agammaglobulinemia: What role does IgG-anti-IgM play?
   - D. Rheumatoid factors (anti-IgG) : What pathogenetic role, if any?

I. REGULATION OF THE IMMUNE RESPONSE

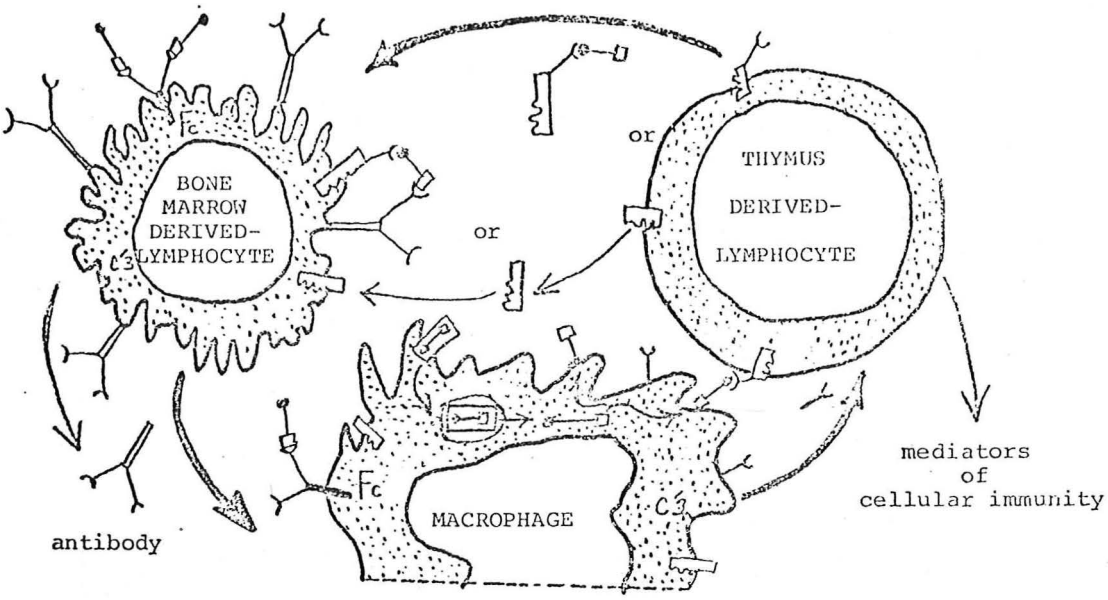

Fig.1 CELL INTERACTIONS IN THE IMMUNE RESPONSE (Ref. 3-35)

= Ir gene product (Associated with histocompatibility HLA or MLC gene products)

= Completed T-Lymphocyte antigen receptor

= Antigen Specific T-helper Factor (Combined with carrier-portion of antigen)

Fig.2 CELLULAR DEVELOPMENT OF THE IMMUNE SYSTEM (Ref. 36-39)

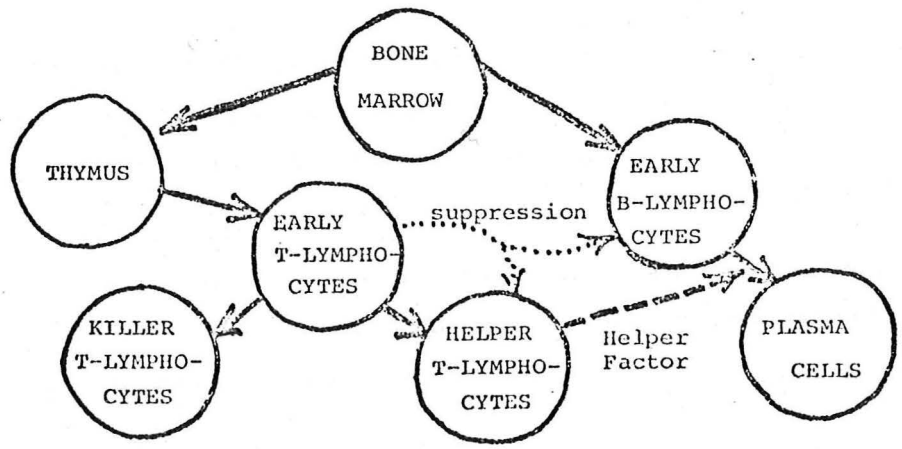

Table I. THYMUS AND T-LYMPHOCYTE FUNCTIONS (Ref. 2)

1. Production of thymosin and other thymic hormones
2. Recognition of the "carrier" portion of certain antigens followed by cell proliferation
3. Release of delayed hypersensitivity mediators after antigen contact
4. Production of antigen-specific "helper" factors which augment the level and quality of antibody produced by B lymphocytes which recognize "hapten" portions of the antigen
5. Recognition of other cells bearing the specific antigen by sensitized T-lymphocytes having direct cytotoxic capacity ("killer" cells)
6. Modulation or suppression of total immune response ("suppressor" cells)
7. Antigen-specific, passive recruitment of other T-lymphocytes by transfer factor

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Fig. 3 GENETIC MAPPING OF HUMAN CHROMASOME # 6 WHICH CONTAINS THE HISTOCOMPATIBILITY-IMMUNE RESPONSE GENE COMPLEX (Ref. 23,24,25)

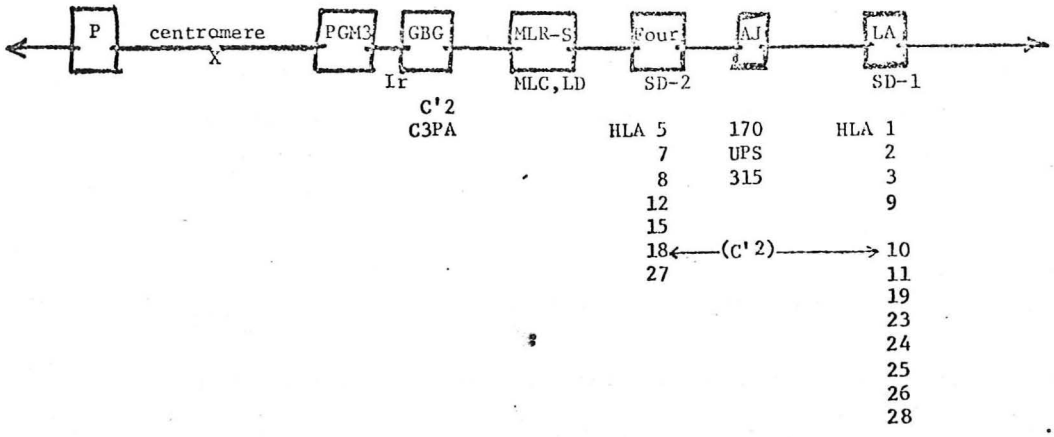


Table II. CLINICAL MEANS OF ASSESSING T-LYMPHOCYTE FUNCTION IN MAN (Ref. 1,2)

1. Delayed hypersensitivity skin testing
2. Spontaneous sheep red cell rosette formation
3. Staining of cell surfaces with fluorescein-labeled antiserum to T-cells
4. One-way mixed lymphocyte cultures (H^3Thymidine uptake into DNA)
5. Mitogen (Con A or PHA) stimulation of lymphocyte cultures (H^3Tdr uptake)
6. Rejection of skin or organ allografts

Table III. PROPERTIES OF SUPPRESSOR, HELPER AND KILLER THYMIC-DERIVED LYMPHOCYTES IN THE MOUSE

Property	Suppressor	Helper	Killer	Reference
Distribution in peripheral blood (% of total lymphocytes)	10-50%	33%	6-8%	37,41
State of differentiation	immature	mature	mature	37
Size, appearence, relative density	medium, pale cytoplasm, low density	small, dark cytoplasm, hi density	small-medium pale cytopl. med. density	38,41, 43
Surface antigens	TL + Ly 1,2,3+	TL neg Ly 1+	TL neg Ly 2,3+	37,42
Histocompatibility differences recognized	?	Ia (MLC) Fc	H2K,H2D	34,37
Effect of adult thymectomy	disappear 6 days	unchanged	unchanged	42
Thymosin activation	++	?	?	59,108
Concanavalin A stimulation	+++	+	+	39,40
Phytohemagglutinin A stimulation	+	+++	+++	39
Cortisol sensitivity	partially resistant	resistant	resistant	41
Anti-thymocyte serum susceptibility (spontaneous autoantibody)	++++	+	?	114,115

Table IV. HUMAN DISEASES INVOLVING ABSENCE OR ABNORMAL FUNCTION OF T-LYMPHOCYTES (Ref. 2,68,86,86,93,97,98)

1. Alymphopenic agammaglobulinemia (Swiss-type, stem cell defect)
2. Thymic aplasia (DiGeorge syndrome)
3. Primary lymphopenic immunologic deficiency (Gitlin-type)
4. Lymphopenia with normal Ig (Nezelof-type)
5. Agammaglobulinemia associated with thymoma (Good)
6. Ataxiatelangectasia (Mrs. Louis Bar syndrome)
7. Sézary syndrome (T-lymphocyte leukemia)
8. Chronic lymphatic leukemia (secondary absence of T-lymphocytes late in the course of the disease)

Table V. DISEASES IN MAN INVOLVING ABNORMAL T-LYMPHOCYTE RECOGNITION OF THE CARRIER PORTION OF ANTIGEN (Ref. 2)

1. α-Methyldopa (Aldomet)-induced hemolytic anemia

2. Goodpasture's syndrome (Hemoptysis, glomerulonephritis and autoantibodies against lung and renal glomerular basement membrane)

3. Thymoma associated autoimmune diseases?
   Polymyositis of severe type, relieved by steroids and followed by myasthenia gravis after thymectomy
   Myasthenia gravis
   Agammaglobulinemia in adults
   Selective red blood cell aplasia
   Systemic lupus erythematosus
   Rheumatoid arthritis (rarely)

II. MUCOCUTANEOUS CANDIDIASIS

Case Report I. [redacted], 19 BM, [redacted], now followed at [redacted] by Dr. James Gilliam. Initially admitted in [redacted], 1973.

This man was noted to have brown scales and crusting on his scalp and white plaques in his mouth by his mother at 3 months of age. At 13 months of age, he was hospitalized with cough and fever. Scalp and mouth cultures grew Candida and Nocardia. Oozing lesions in the genital area suggested the diagnosis of acrodermatitis enteropathica, but little improvement followed treatment with diodoquin.

In the interval prior to his [redacted] 1973 hospitalization, he was admitted to many other hospitals for repeated episodes of right lung pneumonia, and ultimately underwent resection of the right middle lobe and anterior segment of the right upper lobe for bronchiectasis in 1965. He experienced staphylococcal arthritis in 1959 and 1966 which responded to antibiotic therapy, and he has received four courses of amphotericin B for smouldering mucocutaneous candidiasis, the last of which was interrupted in 1969 when he became severely depressed and left the hospital against medical advice. The amphotericin B produced little lasting benefit, and renal toxicity (BUN 27 and creatinine 2.3) accompanied the third course in 1967. His hospitalization in [redacted] 1973 was necessary because of an extensive Candida granuloma which covered most of the skin of his left arm.

At the time of that admission, physical findings included scarred, depigmented alopecia of the scalp, scarring of the lateral face and cheeks, hyperemia with white, curd-like plaques of the tongue, buccal and labial mucosa. There were dystrophic changes of the right middle fingernail. The entire left arm and hand were swollen with erythematous hyperkeratotic plaques and loss of the left distal digits. Similar, but far milder changes were present on the scalp, in the external ears, and in the genital area.

Laboratory data included normal or negative WBC and differential, SMA-12, VDRL, RA latex fixation, antinuclear antibody, LE prep, cryoglobulins, C'H 50 and ASO titer. PBI=6.0, serum cortisol at 8 AM =19μg%, Rubella HI titer 1:64, qualitative immunoelectrophoresis showed sl. increase in IgG and IgA with normal IgM and IgD. Delayed hypersensitivity skin tests for tuberculin, mumps, blastomycosis, histoplasmosis, coccidiomycosis, oidiomycin, trichophytin and streptokinase-streptodornase were all negative. Attempt to sensitize the patient with dinitrochlorobenzene (DNCB, 100 μg) was unsuccessful.

Of four normal siblings, only one showed a close HLA histocompatibility, and he donated lymphocytes for transfusion to the patient. Subsequently, he has responded dramatically, and is now receiving chlortriazole therapy.

Although commonly isolated from humans, Candida albicans rarely causes persistent infections in otherwise healthy subjects. This natural resistance is probably related to natural non-immune barriers, in part, but the high percentage of persons with strong cellular immunity to candida extracts by skin testing suggests that acquired immunity also is required to keepthe fungus on a commensal level. Endocrine abnormalities, such as hypoparathyroidism, hypothyroidism or Addison's disease, immunosuppression or broad-spectrum antibiotic therapy commonly lead to secondary candida infections, suggesting that the host-commensal balance is rather delicate. A relatively minor defect in either the non-specific or specific protective mechanism may alter this balance in favor of the fungus which then becomes parasitic (Ref. 69).

Table VI. IMMUNE ABNORMALITIES ASSOCIATED WITH CHRONIC MUCOCUTANEOUS CANDIDIASIS (Ref. 69,71, 74,75)

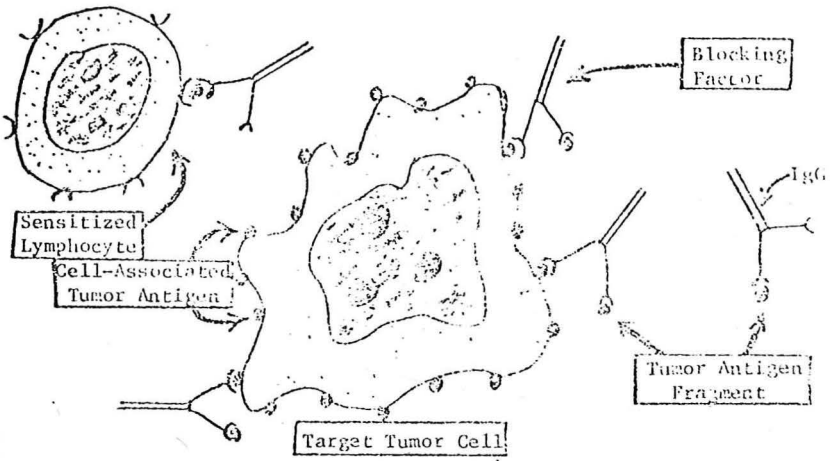
Immune Function	Type			
	I	II	III	IV
MIF* release in vitro after candida antigen added to patient's lymphocytes	(-)	(-)	+	+
H^3Tdr*uptake into DNA after candida antigen added to patient's lymphocytes in vitro	+	(-)	+	+
"Blocking factor" present in patient's plasma which prevents DNA synthesis or MIF release after antigen added to patient's or normal sensitive lymphocytes in vitro	-	(+)	-	-
Macrophage migration (pt's cells) to antigen-stimulated lymphocyte chemotactic factor or C5a	+	+	(-)	+

* MIF= macrophage migration inhibitory factor
*H^3Tdr= Tritiated Thymidine deoxyribotide
(-) = Significant abnormalities are circled.

Our patient, [redacted], proved to be identical to Type II above, and failed to respond when his lymphocytes were incubated in vitro with candida antigen, and his serum contained a blocking factor which prevented H^3-Tdr uptake by DNA of normal lymphocytes known to be strongly reactive to Candida in the presence of normal serum when tested by Dr. Robert Johnson of the Rheumatic Diseases Unit. Mucocutaneous candidiasis (some patients) joins many human neoplasms (Ref. 76), chronic viral infections (Ref. 78) and possibly multiple sclerosis (Ref. 79) and systemic lupus erythematosus (Ref. 80) in having serum "blocking factors" which suppress T-lymphocyte reactions to specific antigens. Increasing evidence suggests that these "blocking factors" are complexes between high-affinity IgG antibody and small antigen fragments. A suggested mechanism for this T-cell suppression is illustrated in Fig. 4 on page 7. Sjögren, et al, describe the separation of one of these blocking factors into free IgG antibody and an antigen fragment after acid dissociation in Ref. 76.

Not all soluble "blocking factors" which suppress delayed hypersensitivity or block other T-lymphocyte functions are composed of immunoglobulin with or without antigen. Mackaness (Ref. 64) and Gatti (Ref. 77) have described non-antibody factors which depress delayed hypersensitivity and the mixed lymphocyte culture (MLC) reactions, respectively.

Fig. 4. MECHANISM BY WHICH BLOCKING FACTOR MAY PROMOTE TUMOR GROWTH



III. ACQUIRED HYPOGAMMAGLOBULINEMIA -Suppressor T-Lymphocytes in Man

Recently, Blaese, et al, made the surprising discovery that induced agammaglobulinemia in the chicken was associated with a T-lymphocyte suppression capable of blocking normal immunoglobulin synthesis by untreated chicken lymphocytes (Ref. 81). They termed this "infectious" agammaglobulinemia since it could be transmitted in vivo to normal adult chickens by infusing 4 month old chick marrow cells from agammaglobulinemic donors, and the previously normal recipients would develop a progressive humoral immunodeficiency and agammaglobulinemia.

Waldmann, Blaese, et al (Ref. 82), then examined a group of 8 patients with common variable hypogammaglobulinemia by culturing their peripheral blood lymphocytes with poke weed mitogen which is known to be a non-specific stimulant for B-lymphocytes to differentiate and produce immunoglobulin. Unlike normal peripheral blood lymphocytes, none of the patients' lymphocytes produced significant immunoglobulin after such stimulation. However, when their lymphocytes were fractionated to remove T-lymphocytes and the remaining B-lymphocyte population then cultured with poke weed mitogen, normal amount of immunoglobulin was produced. In addition, when all the 8 patients' lymphocytes were co-cultured with lymphocytes from normal persons along with poke weed mitogen, the usual immunoglobulin synthesis of the normal B-lymphocytes was almost completely suppressed in 5 of the 8 cultures. To rule out some effect of the histoincompatibility of the patients' lymphocytes and the normal donor lymphocytes, 22 pairs of normal unrelated donors were co-cultured in vitro with poke weed mitogen, and in every instance no suppression of immunoglobulin synthesis was observed in spite of the anticipated mixed lymphocyte reactions, due to histoincompatibility. An example of their results is shown in Table VII below.

Table VII. INHIBITION OF IMMUNOGLOBULIN SYNTHESIS BY NORMAL LYMPHOCYTES WHEN CO-CULTURED WITH LYMPHOCYTES FROM A PATIENT WITH HYPOGAMMAGLOBULINEMIA

	IgG	IgA	IgM	Average %
	(ng. per culture)			Inhibition
Hypogammaglobulinemia pt. alone	0	0	26	
Control subject A alone	1640	640	2860	
Co-culture pt. + Control A	0	14	400	95

2×10^6 lymphocytes from each donor + poke weed mitogen for 7 days

A significant question is the type of immunodeficiency which is present in an adult or child in whom recurrent severe infections have occurred. Fig. 5 and Fig. 6 below outline a systematic approach to this problem as developed by Bellanti (Ref. 83)

Fig. 5. SCHEME OF APPROACH IN THE INVESTIGATION OF AN ADULT WHO PRESENTS WITH REPEATED INFECTIONS

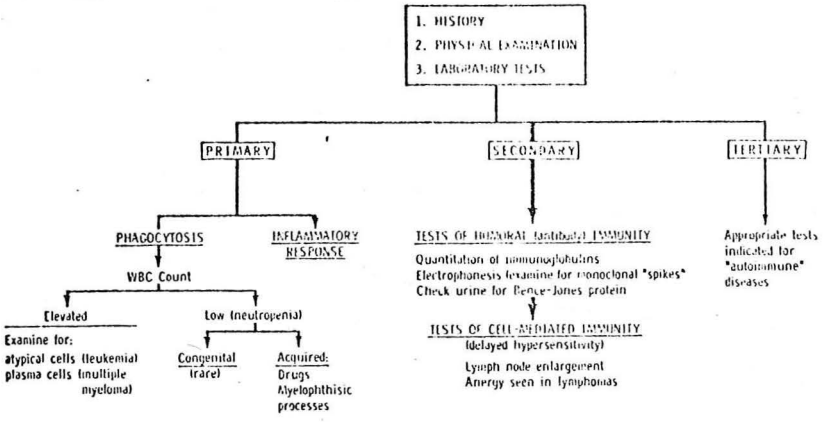
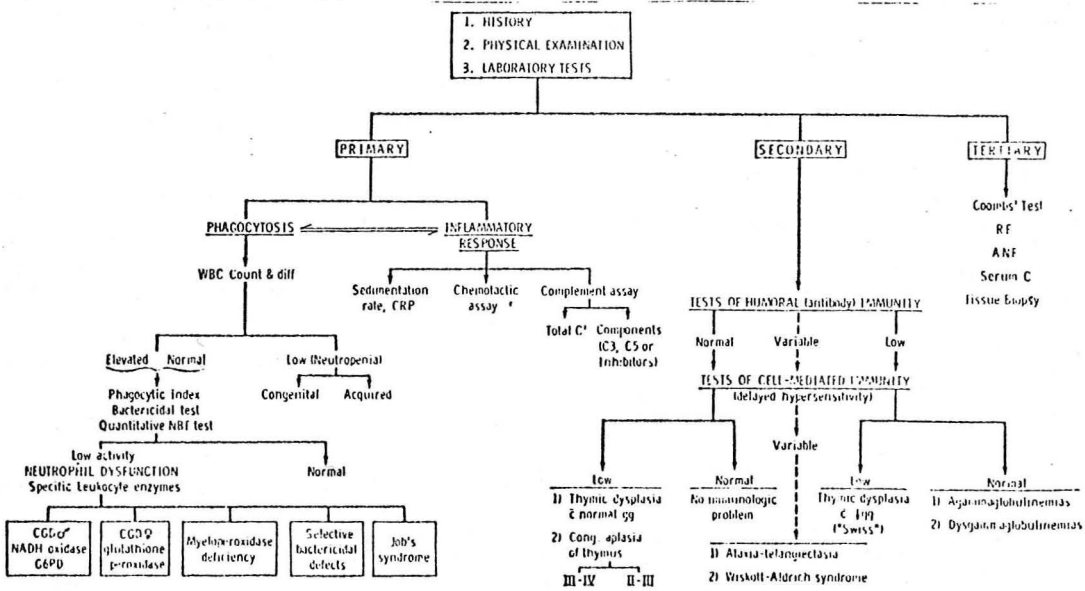


Fig. 6. SCHEME OF APPROACH IN THE INVESTIGATION OF THE INFANT WHO PRESENTS WITH REPEATED INFECTIONS



IV. NORMAL PREGNANCY, NEOPLASIA AND ATAXIATELANGIECTASIA (Ref. 68, 84-87)

The fetal circulation contains several embryo-specific proteins which are present in the serum of adult individuals in very low concentrations. Among these is alpha-feto-protein which may reach a level of 4 mg/ml during early to mid-gestation, then falls to the normal adult level of approximately 40 ng/ ml (.001% of the maximum fetal level).

The recent studies of Murgita and Tomasi (Ref 68) have shown that alpha-feto-protein is a potent inhibitor of T-lymphocyte function , and can thus indirectly inhibit both primary and secondary antibody responses in concentrations as low as 1 µg/ml. It had its most impressive effect in inhibiting the IgG secondary response, but most parameters of immune response were somewhat inhibited. No cytotoxicity was found to accompany this inhibition of immunity.

Since a number of neoplasms, particularly hepatoma, stomach, and pancreas have been associated with abnormal appearence of alpha-fetoprotein in the patients' sera, these recent findings of immune suppression by this protein have raised the possibility of a pathogenetic role in the neoplasia in these patients (Ref. 85).

Waldmann and McIntire (Ref. 86) recently noted that patients with ataxiatelangiectasia who have thymic immunodeficiency, occasional absence of IgA, and a marked increase in a variety of cancer, uniformly show significant elevations of serum alpha-fetoprotein. This protein is elevated for years prior to the appearence of tumors, but could well represent the mechanism of loss of normal immune surveillance which so strongly predisposes these patients to cancer development.

ATAXIATELANGIECTASIA

Case Report II. [redacted], 9 1/2 year old WF, [redacted], seen by Dr. Morris Ziff on [redacted]-68.

This 9 1/2 year old girl had had symptoms of weakness, trouble with gait, developing ataxia and dysarthria and internal strabismus with repeated attacks of upper respiratory infections over the entire period of her childhood with the first abnormalities noted about 6 months of age. She also has a 3 1/2 year old brother who also is affected, and a half-brother on the paternal side said to have cerebral palsy.

On examination, the patient was small , dysarthric and had telangiectasias on the bulbar conjunctivae and the lower palpebral conjunctivae bilaterally.

There were three small cafe-au-lait spots over the left knee. Neurological showed nystagmus, cerebellar dysfunction and gait problems, with spontaneous choreiform movements. She elevated her arms in a choreo-athetoid type of posture, and milked her fingers aimlessly. Laboratory data showed Hgb= 12.1 gm%, WBC= 3,100, polys 53, lymphocytes 40%, urine normal, cerebrospinal fluid normal, IgA 104 mg% (nl= 70-350 mg%). Her brother showed no IgA on radial diffusion assay. Skin tests negative.

This patient was seen prior to the observation of the elevated alpha-fetoprotein in the serum in ataxiatelangiectasia, and this determination was not made.

V. LYMPHOPROLIFERATIVE DISORDERS (Ref. 88-99)

Sjögren's syndrome was originally described as dry eyes, dry mouth and rheumatoid arthritis. In recent years, however, it has become apparent that it can exist without necessarily having associated rheumatoid arthritis, but may be seen with lymphoma-like variations, and with scleroderma, systemic lupus erythematosus, or in isolation, although most patients do have some form or other of identifiable rheumatic disease. It has recently been possible to study the lymphocytes which infiltrate the salivary and lacrimal glands of Sjögren's patients by means of lip biopsies of the labial salivary glands. These are well-tolerated by the patients and are of considerable value diagnostically in establishing the character of the lymphoproliferative disorder which is present in any given patient.

Clinical and pathological evidence suggests that a wide spectrum of lymphoproliferation exists in Sjögren"s syndrome-SS, from benign disease with lymphoid infiltrates confined to glandular tissue on the one end, to widespread lymphoreticular malignancy on the other. In the middle of the spectrum are patients threatened by extraglandular extension of lymphoproliferation which is not clinically or histologically malignant and which apparently has the potential to regress with appropriate therapy or to progress to frank neoplasia. Case reports in the literature associate SS with pseudolymphoma, Waldenström's macroglobulinaemia, reticulum cell sarcoma, or other lymphomas. Similar lymphoproliferative processes have been observed in other autoimmune diseases, in certain immune deficiency states, with hydantoin and other anticonvulsant drugs, and in experimental animal models (Ref. 89,90). In SS, as in these other conditions, it seems likely that a combination of genetic, immunologic, and viral or other unknown environmental factors plays a role in pathogenesis.

The fascinating observation that thymosin corrects the abnormally high cell turnover in the NZB mouse thymus population in an animal model, which like SS has a marked tendency to convert to lymphoma, suggests that the role of the T-suppressor cell in SS should be further investigated (See Ref. 92).

Two additional interesting observations in human lymphoproliferative disorders have recently been made. The Sézary syndrome, a form of T-lymphocyte leukemia associated with skin infiltration resembling and perhaps identical to forms of mycosis fungoides, has been shown to retain differentiated T-cell function including the elaboration of MIF into the patient's serum (Ref. 97, 98), and helper factor.

In addition, Broder, and his colleagues (Ref. 99) have shown that peripheral blood cells from patients with multiple myeloma are potent suppressors of normal B-lymphocyte immunoglobulin synthesis when co-cultured with such normal lymphocytes in the presence of poke weed mitogen. They have tentatively identified the source of this suppression as blood monocytes in the circulation of myeloma patients. This observation provides an interesting explanation for the "functional agammaglobulinemia" which is observed clinically in multiple myeloma patients who so often fall victim to pneumoccal infections and other similar organisms.

VI. SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) (Ref. 100-110)

Whether patients with SLE are over-responders or under-responders is a clinically important issue. In spite of the hyperglobulinemia present in most SLE patients, they have a marked problem with severe infections with about one-third dying of this problem. Studies by Zingale (Ref. 100) using a thymus-dependent antigen, isologous erythrocytes, suggested that they are over responders. On the other hand, Baum and Ziff (Ref. 101) found that the SLE patients whom they studied made only half as much antibody to bacterial antigens as normal controls. It should be emphasized that these bacterial antigens (brucella and E. coli extracts) were thymus-independent antigens which we now know are recognized in quite different manners by the immune system, and this may account for the apparent divergent results of these two studies.

The observations that the NZB/W model of SLE in the mouse show progressive depletion of the T-suppressor population provides a good explanation for the appearence of the variety of autoantibodies seen in SLE. The release from T-suppression permits the recognition of self-antigens and production of autoantibodies leading to hemolytic anemia and renal disease in this animal model of SLE. Greatly increased B-cell proliferation in these animals might also explain the high frequency of lymphoma which is found in older animals.

Table VIII. MECHANISMS FOR AUTOIMMUNITY IN SLE

A. Loss of tolerance to self antigens
   1. Imbalance of regulation of the immune system on a genetic basis
   2. Viral infection of the thymus

B. Accidental immunization
   1. "Self + X" (X= drug, food,etc)
   2. Innocent bystander for tumor or viral-induced antigens on cells
   3. Coating of cell surface receptors with specific antibody:foreign antigen complexes
   4. Digestion of portions of normal tissue components during inflammation to produce foreign antigens

C. Release of antigen from a restricted or immunologically privileged site

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Table IX. DOES DEFICIENCY OF THYMIC IMMUNE SUPPRESSOR FUNCTION CAUSE SLE?

1. Neonatal thymectomy in NZB/W mice causes accelerated autoimmunity and early death

2. Adult thymectomy in patients with myasthenia gravis is often followed by an SLE-like clinical syndrome

3. Young thymus cell infusions retard the appearance of antinuclear antibodies in strain A mice

4. Food antigens cause higher antibody responses in some SLE patients than in matched controls without SLE

5. Anti-thymocyte serum markedly enhances anti-double stranded RNA in NZB/W mice 1 to 3 months of age

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VII. AUTOANTIBODIES CAN ENHANCE OTHER FORMS OF IMMUNE ABNORMALITY (Ref. 112-119)

One of the most logical explanations for the loss of T-suppressor lymphocytes in SLE and in the NZB/W model of SLE is the early development of thymus-specific autoantibodies (Ref.111, 112, 115). That such antibodies are known to cross-react with brain tissue in the case of anti-θ antigen in mouse thymocytes is intriguing in the patient population with SLE. A recent report that anti-thymocyte reactive antibodies are found in schizophrenic patients (Ref. 113) would be compatible with this type of cross-reactivity, also.

Table X. FREQUENCY OF CYTOTOXIC REACTIONS WITH A PANEL OF ALLOGENEIC LYMPHOCYTES AMONG 36 REACTIVE SLE SERUMS* (Ref. 111)

	Per Cent of Lymphocyte Panel			
	10%	10-20%	20-40%	40%
Number of serums reacting	17	9	6	4
% of serums reacting	47%	25%	17%	11%

*Obtained from 36 individual patients.

Various autoantibodies which are directed against the separate classes of immunoglobulins are potentially capable of altering the cells which bear these proteins on their surfaces. Two isolated reports are particularly interesting in this regard.

Williams, et al, (Ref. 117) observed that 53% of atopic patients (asthma, hay fever or eczema) had IgM anti-IgE autoantibodies which occurred spontaneously in their serum compared to 8.5% of miscellaneous control patients. These antibodies only reacted with IgE after its combination with antigen, and appeared to vary in their affinity for different IgE preparations, suggesting possible allotype specificity reminescent of the reaction with Gm and Inv allotypes of IgG by various rheumatoid factors.

Table XI. APPARENT POTENTIATION OF HISTAMINE RELEASE BY 19S HUMAN ANTI-γE USING ALLERGIC PATIENT'S LEUKOCYTES

Fraction or sample studied	Basic anti-γE titer	Total per cent histamine released
		%
Bermuda allergen alone, 0.001 μg	0	0
Fl. 19S (allergic patient)	1:16	0
Bermuda allergen 0.001 μg plus Fl. 19S	1:16	39.6
Bermuda allergen 0.001 μg plus Jo. 19S	0	0
Rabbit anti-γE 1:1000	1:32	18.1

The other report by Abdou, et al (Ref. 117) found that patients with acquired agammaglobulinemia, in contrast to patients with infantile agammaglobulinemia, had normal numbers of immunoglobulin receptors on their bone marrow cells, but showed marked decrease in these receptors on peripheral blood lymphocytes. In addition, the patients with acquired agammaglobulinemia had an IgG-anti-IgM antibody in their serum which was believed responsible for the depressed Ig synthesis in these patients.

The measurement, clinical distribution and pathological implications of rheumatoid factors has been summarized in Ref. 119. The formation of mixed cryoglobulins which lead to glomerulonephritis or other forms of vasculitis represent the principal pathogenic potential of anti-IgG autoantibodies found in human disease.

REFERENCES

General Reviews

1. Miller, F., Applications of immunology to understanding mechanisms of human disease, Federation Proc. 34, 1635(1975).

2. Osoba, D., Thymic function, immunologic deficiency, and autoimmunity, Medical Clinics of North America 56, 319(1972).

3. Green, I., Genetic control of immune responses, Immunogenetics 1, 4(1974).

4. Katz, D.H. and B. Benacerraf, The function and interrelationships of T-cell receptors, Ir genes and other histocompatibility gene products, Transplant. Rev. 22, 175(1975).

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5. Singer, S.J., Molecular biology of cellular membranes with applications to immunology, Advances in Immunology 19, 1(1974).

6. Polliack, A., N.Lampen, B.D. Clarkson, E.DeHarven, Z.Bentwich, F.P.Siegal and H.G.Kunkel, Identification of human B and T lymphocytes by scanning electron microscopy, J. Exptl. Med. 138, 607 (1973).

7. Claman, H.N. and E.A. Chaperon, Immunologic complementation between thymus and marrow cells. A model for the two-cell theory of immunocompetence, Transplant. Rev. 1, 92(1969).

8. Möller, G. and A.Coutinho, Role of C3 and Fc receptors in B-lymphocyte activation, J. Exptl. Med. 141, 647(1975)

9. Katz, D. and E.R. Unanue, Critical role of determinant presentation in the induction of specific responses in immunocompetent lymphocytes, J. Exptl. Med. 137, 967(1973).

10. Rosenthal, A.S., P.E. Lipsky and E.M. Shevach, Macrophage-lymphocyte interaction and antigen recognition, Federation Proc. 34, 1743(1975).

11. Davie, J.M. and W.E. Paul, Immunological maturation. Preferential proliferation of high affinity precursor cells, J. Exptl. Med. 137, 201(1973).

12. Hoffmann, M. and J.W. Kappler, Regulation of the immune response II. Qualitative and quantitative differences between thymus and bone marrow-derived lymphocytes in the recognition of antigen, J. Exptl. Med. 137, 721(1973).

13. Bystryn, J-C, G.W. Siskind and J.W. Uhr, Binding of antigen by immunocytes II. Effect of specific antigen on binding by MOPC 315 cells, J.Exptl. Med. 141, 1227(1975).

14. Unanue, E.R., Antigen binding cells II. Effect of highly radioactive antigen on the immunologic function of bone marrow cells,

14.(cont'd) J.Immunol. 107, 1663(1971).

15. Basten, A., J.F.A.P. Miller and R. Abraham, Relationship between Fc receptors, antigen-binding sites on T and B cells, and H-2 complex-associated determinants, J.Exptl. Med. 141, 547(1975)

16. LaGrange, P.H., G.B. Mackaness and T.E. Miller, Influence of dose and route of antigen injection on the immunological induction of T-cells, J.Exptl. Med. 139, 528(1974).

17. Semyk, G., E.B.Williams, D.E.Nitecki and J.A.Goodman, The functional dissection of an antigen molecule: Specificity of humoral and cellular immune response to glucagon, J. Exptl. Med. 133, 1294(1971).

18. Karniely, Y., E.Mozes, G.M.Shearer and M.Sela, The role of thymocytes and bone marrow cells in defining the response to the dinitrophenyl hapten attached to positively and negatively charged synthetic polypeptide carriers. Cell fractionation over charged columns, J. Exptl. Med. 137, 183(1973).

19. Liew, F.Y. and C.R.Parish, Lack of a correlation between cell-mediated immunity to the carrier and the carrier-hapten helper effect, J. Exptl. Med. 139, 779(1974).

20. Watson, J., E. Trenkner and M.Cohn, The use of bacterial lipopolysaccharides to show that two signals are required for the induction of antibody synthesis, J. Exptl. Med. 138, 699(1973).

21. Coutinho, A. and E.Gronowicz, Genetical control of B-cell responses III. Requirement for functional mitogenicity of the antigen in thymus-independent specific responses, J. Exptl. Med. 141, 753 (1975).

22. Louis, J.A., J.M.Chiller and W.O. Weigle, The ability of bacterial lipopolysaccharide to modulate the induction of unresponsiveness to a state of immunity. Cellular parameters, J. Exptl. Med. 138, 1481(1973).

23. Svezgaard, A., P.Platz, L.P.Ryder, L.S.Nielson and M.Thomsen, HL-A and Disease associations - a survey, Transpl. Rev. 22,3(1975).

24. Fu, S.M., H.G.Kunkel, H.P.Brusman, F.H.Allen,Jr. and M.Fotino, Evidence for linkage between HL-A histocompatibility genes and those involved in the synthesis of the second component of complement, J. Exptl. Med. 140, 1108(1974).

25. Ferreira, A. and V.Nussenzweig, Genetic linkage between serum levels of the third eomponent of complement and the H-2 complex, J. Exptl. Med. 141, 513(1975).

26. Oldstone, M.B.A., F.J.Dixon, G.M.Mitchell and H.O.McDevitt, Histocompatibility-linked genetic control of disease susceptibility. Murine lymphocytic choriomeningitis virus infection, J. Exptl. Med. 137, 1201(1973).

27. Hämmerling, G.J., T.Masuda and H.O. McDevitt, Genetic control of the immune response. Frequency and characteristics of antigen-binding cells in high and low responder mice, J. Exptl. Med. 137,1180(1973).

28. Kapp, J.A., C.W.Pierce and B.Benacerraf, Genetic control of immune responses in vitro I. Development of primary and secondary plaque-forming cell responses to the random terpolymer L-Glutamic acid^{55}-L-Alanine^{30}-L-Tyrosine^{10} (GAT) by mouse spleen cells in vitro, J. Exptl. Med. 138, 1107(1973).

29. Ibid, Ref. 28 III. Tolerogenic properties of GAT for spleen cells from nonresponder ($H2^5$ and $H2^2$) mice, J. Exptl. Med. 140, 172(1974).

30. Katz, D.H., M.Graves, M.E.Dorf, H.Dimuzio and B.Benacerraf, Cell interactions between histoincompatible T and B lymphocytes VII. Cooperative responses between lymphocytes are controlled by genes in the I region of the H2 complex,J.Exptl. Med. 141, 263 (1975).

31. Ben-Sasson,S.Z., E.Shevach, I.Green and W.E.Paul, Alloantiserum-induced inhibition of migration inhibition factor production in immune response gene-controlled immune systems, J. Exptl. Med. 140, 383(1974).

32. Fathman, C.G., B.S.Handwerger and D.H.Sachs, Evidence for a role of Ir-associated alloantigens in mixed lymphocyte culture stimulation, J. Exptl. Med. 140, 853(1974).

33. Finkelman, F.D., E.M.Shevach, E.S.Vitetta, I.Green and W.M. Paul, Guinea pig immune response-related histocompatibility antigens. Partial characterization and distribution, J. Exptl. Med. 141, 27, (1975).

34. Dickler, H.B. and D.H.Sachs, Evidence for identity or close association of the Fc receptor on B lymphocytes and alloantigens determined by the Ir region of the H2 complex, J. Exptl. Med. 140,779(1974).

35. Grey, H.M., R.T.Kubo, S.M.Colon, M.D.Poulik, P.Cresswell, T. Springer, M.Turner and J.L.Strominger, The small subunit of HL-A antigen is β2-microglobulin, J. Exptl. Med. 138, 1608(1973).

36. Gershon, R.K., T cell control of antibody production, Contemporary Topics in Immunobiology 3, 1(1973).

37. Cantor,H. and E.A.Boyse, Functional subclasses of T lymphocytes bearing different Ly antigens I. The generation of functionally distinct T-cell subclasses in a differentiative process independent of antigen, J. Exptl. Med. 141, 1376(1975); and II. Cooperation between subclasses of Ly+ cells in the generation of killer activity, J. Exptl. Med. 141, 1390(1975).

38. Matter, A. The differentiation pathway of T-lymphocytes. Evidence for two diffenentiated cell types, J. Exptl. Med. 140, 566(1974).

39. Dutton, R.W., Inhibitory and stimulatory effects of concanavalin A on the response of mouse spleen cell suspensions to antigen, J. Exptl. Med. 138, 1496(1973).

40. Rich, R.R. and C.W.Pierce, Biological expressions of lymphocyte activation II. Generation of a population of thymus-derived suppressor lymphocytes, J. Exptl. Med. 137, 649(1973).

41. Ha, T-Y, B.H.Waksman and H.P.Treffers, The thymic suppressor cell I. Separation of subpopulations with suppressor activity, J. Exptl. Med. 139, 13(1974).

42. Bach, J-F. and M.Dardenne, Antigen recognition by T lymphocytes III. Evidence for two populations of thymus-dependent rosette-forming cells in spleen and lymph nodes, Cellular Immunol. 6, 394(1973).

43. Elliott, B.E., J.S.Haskill and M.A.Axelrad, Rosette-forming ability of thymus-derived lymphocytes in cell-mediated immunity I. Delayed hypersensitivity and in vitro cytotoxicity, J. Exptl. Med. 141, 584(1975); and II. Helper cell activity, J. Exptl. Med, 141,600(1975).

44. Tada, R. and R.Takemori, Selective roles of thymus-derived lymphocytes in the antibody response I. Differential suppressive effect of carrier-primed T-cells on hapten-specific IgM and IgG antibody responses, J. Exptl. Med. 140, 239(1974); and II. Preferential suppression of high-affinity antibody-forming cells by carrier-primed suppressor T-cells, J. Exptl. Med. 140,253(1974).

45. Herzenberg, L.A., E.L.Chan, M.M.Ravitch, R.J.Riblet and L.A. Herzenberg, Active suppression of immunoglobulin allotype synthesis, J. Exptl. Med. 137, 1311(1973).

46. Baker, P.J., N.D.Reed, P.W.Stashak, D.F.Amsbaugh and B.Prescott, Regulation of the antibody response to type III pneumococcal polysaccharide I. Nature of regulatory cells, J. Exptl. Med. 137,1431(1973).

47. Mosier, D.E. and B.M.Johnson, Ontogeny of mouse lymphocyte function II. Development of the ability to produce antibody is modulated by T lymphocytes, J. Exptl. Med. 141, 216(1975).

48. Chiller, J.M., J.A.Louis, B.J.Skidmore and W.O.Weigle, Cellular parameters of the tolerant state induced to human γ-globulin in mice and its modulation by bacterial lipopolysaccharide, in Immunological Tolerance: Mechanism and Potential Therapeutic Applications, D.H.Katz and B.Benacerraf, eds., Academic Press, Inc., New York 1974.

49. Benjamin, D.C., Evidence for specific suppression in the maintenance of immunologic tolerance, J. Exptl. Med. 141,635(1975).

50. C.W.Fink, W.E.Miller, D.Dorward and J.LoSpalluto, The formation of macroglobulin antibodies II. Studies on neonatal infants and older children, J. Clin. Invest. 41:7, 1422(1962).

51. Abrahams, S., R.A.Phillips and R.G.Miller, Inhibition of the immune response by 7S antibody. Mechanism and site of action, J. Exptl. Med. 137, 870(1973).

52. Birnbaum, G., M.E.Weksler and G.W.Siskind, Demonstration of an antibody-mediated tolerance state and its effect on antibody affinity, J. Exptl. Med. 141, 411(1975).

53. Henry, C.,and N.K.Jerne, Competition of 19S and 7S antigen receptors in the regulation of the primary immune response. J. Exptl. Med. 128, 133(1968).

54. Mackaness, G.B. and P.H.LaGrange, Restoration of cell-mediated immunity to animals blocked by a humoral response, J. Exptl. Med. 140, 865(1974).

55. Basten, A., J.F.A.P.Miller, J.Sprent and C.Cheers, Cell-to-cell interaction in the immune response X. T-cell dependent suppression in tolerant mice, J. Exptl. Med. 140, 199(1974).

56. Phillips, S.M. and T.Wegmann, Active suppression as a possible mechanism of tolerance in tetraparental mice, J. Exptl. Med. 137, 291(1973).

57. vonBoehmer, H., J.Sprent and M.Nabholz, Tolerance to histocompatibility determinants in tetraparental bone marrow chimeras, J. Exptl. Med. 141, 322(1975).

58. Elkins, W.L., Deficit of specific thymus-dependent lymphocytes in transplantation tolerance in the rat, J. Exptl. Med.137, 1097(1973).

59. Bach,J-F., M.Dardenne, A.L.Goldstein,A.Guha, and A.White, Appearance of T-cell markers in bone marrow rosette-forming cells after incubation with thymosin, a thymic hormone, Proc. Nat. Acad. Sci. USA 68, 2734(1971).

60. Armerding, D. and D.H.Katz, Activation of T and B lymphocytes in vitro II. Biological and biochemical properties of an allogeneic effect factor (AEF) active in triggering specific B lymphocytes, J. Exptl. Med. 140, 19(1974).

61. Taussig, M.J., E.Mozes and R.Isac, Antigen-specific thymus cell factors in the genetic control of the immune response to poly-(Tyrosyl, Glutamyl)-Poly-D-L-Alanyl-Poly-Lysyl,J.Exptl. Med. 140, 301(1974).

62. Ambrose, C.T., Regulation of the secondary antibody response in vitro II. Chemical properties of an antibody inhibitory material (AIM) produced in antigen-stimulated rabbit lymph node organ culture, J. Exptl. Med. 137, 1369(1973).

63. Geha, R.S.,E.Schneeberger, F.S.Rosen and E.Merler, Interaction of human thymus-derived and non-thymus-derived lymphocytes in vitro. Induction of proliferation and antibody synthesis in B lymphocytes by a soluble factor released from antigen-stimulated T lymphocytes, J. Exptl. Med. 138, 1230(1973).

64. Mackaness, G.B., P.H.LaGrange, T.E.Miller and T. Ishibashi, Feedback inhibition of specifically sensitized lymphocytes, J. Exptl. Med. 139, 543(1974).

65. Calderon, J., J-M.Kiely, J.L.Lefko and E.R.Unanue, The modulation of lymphocyte functions by molecules secreted by macrophages. J. Exptl. Med. 142, 151(1975).

66. Aschev, M.S., W.J.Schneider, F.T.Valentine, and H.S. Lawrence, In vitro properties of leukocyte dialysates containing transfer factor, Proc.Nat. Acad. Sci. USA 71,1178(1974).

67. Mortensen, R.F., A.P.Osmand and H. Gewurz, Effects of C-reactive protein on the lymphoid system I. Binding to thymus-dependent lymphocytes and alteration of their functions, J. Exptl. Med. 141, 821(1975).

68. Murgita, R.A. and T.B.Tomasi,Jr., Suppression of the immune response by α-fetoprotein I. The effect of a mouse α-fetoprotein on the primary and secondary antibody response, J. Exptl. Med. 141, 269(1975); and II. The effect of mouse α-fetoprotein on mixed lymphocyte reactivity and mitogen-induced lymphocyte transformation, J. Exptl. Med. 141, 440(1975).

II. Mucocutaneous Candidiasis

69. Valdimarsson, H., J.H.Higgs, R.S.Wells, M.Yamamura, J.R.Hobbs and P.J.L.Holt, Immune abnormalities associated with chronic mucocutaneous candidiasis, Cell. Immunol. 6,348(1973).

70. Kirkpatrick, C.H., R.R.Rich, R.G.Graw,Jr., T.K.Smith, I.Mickenberg and G.N.Rogentine, Treatment of chronic mucocutaneous moniliasis by immunologic reconstitution, Clin. Exp. Immunol. 9,733(1971).

71. Marmor, M.F. and E.V. Barnett, Cutaneous anergy without systemic disease. A syndrome associated with mucocutaneous fungal infection, Am. J. Med. 44, 979(1968).

72. Canales,L., R.O.Middlemas, III, J.M.Louro and M.A.South, Immunological observations in chronic mucocutaneous candidiasis, Lancet 2, 567(1969).

73. Patterson, P.Y., R.Semo, G.Blumenschein and J.Swelstad, Mucocutaneous candidiasis, anergy and a plasma inhibitor of cellular immunity: Reversal after amphotericin B therapy, Clin. Exp. Immunol. 9, 595(1971).

74. Kirkpatrick, C.H., R.R.Rich and J.E.Bennett, Chronic mucocutaneous candidiasis: Model-building in cellular immunity, Ann. Int. Med. 74, 955(1971).

75. Snyderman, R., L.C. Altman, A.Frankel and R.M.Blaese, Defective monomuclear leukocyte chemotaxis: A previously unrecognized immune dysfunction. Studies in a patient with chronic mucocutaneous candidiasis, Ann. Int. Med. 78, 509(1973).

76. Sjögren, H.O., I.Hellström, S.C.Bansal and K.E.Hellström, Suggestive evidence that the "blocking antibodies" of tumor-bearing individuals may be antigen-antibody complexes, Proc. Nat. Acad. Sci. USA 68, 1372(1971).

77. Gatti, R.A., E.J. Yunis and R.A.Good, Characterization of a serum inhibitor of MLC reactions, Clin. Exp. Immunol. 13,427(1973).

78. Amed, A., D.M.Strong, K.W.Sell, G.B.Thurman, R.C.Knudsen, R. Wistar,Jr. and W.R.Grace, Demonstration of a blocking factor in the plasma and spinal fluid of patients with subacute sclerosing panencephalitis, J. Exptl. Med. 139, 902(1974).

79. Untermohlen, V. and J.B.Zabriskie, A suppression of cellular immunity in patients with multiple sclerosis, J. Exptl. Med. 138, 1591(1973).

80. Untermohlen,V., J.B.Winfield, J.B.Zabriskie and H.G.Kunkel, A depression of cell-mediated immunity to measles antigen in patients with systemic lupus erythematosus, J.Exptl. Med. 139, 1019(1974).

III. Acquired Hypogammaglobulinemia

81. Blaese, R.M., P.L.Weiden, I.Koski and N.Dooley, Infectious agammaglobulinemia: Transmission of immunodeficiency with grafts of agammaglobulinemic cells, J. Exptl. Med. 140,1097 (1974).

82. Waldmann,T.A., M.Durm, S.Broder, M.Blackman, R.M.Blaese and W. Strober, Role of suppressor T cells in pathogenesis of common variable hypogammaglobulinemia, Lancet 2, 609(1974).

83. Bellanti, J.A., Immunology, W.B.Saunders Co., New York, 1971, pp.537,540.

IV. Normal Pregnancy, neoplasia and ataxiatelangectasia

84. Masopust, J., V.Zizkovsky and K.Kithier, Fetoproteins in different species of mammals. Protides Biol. Fluids Proc. Colloq. 18, 63(1971).

85. Abelev, G.I., Alpha-fetoprotein in oncogenesis and its association with malignant tumors, Adv. Cancer Res. 14, 295(1971).

86. Waldmann, T.A., and K.R.McIntire, Serum alpha-fetoprotein levels in patients with ataxia telangectasia, Lancet 2,1112 (1972).

87. Peterson, R.D.A., W.D.Kelly and R.A.Good, Ataxiatelangectasia, Its association with defective thymus, immunological deficiency disease, and malignancy, Lancet 2, 1189(1964).

V. Lymphoproliferative disorders

88. Talal, N., L.Sokoloff and W.F.Barth, Extrasalivary lymphoid abnormalities in Sjögren's syndrome (Reticulum cell sarcoma,

88. (cont'd) "pseudolymphoma", macroglobulinemia), Am.J. Med. 43, 50(1967)

89. Anderson, L.G. and N.Talal, The spectrum of benign to malignant lymphoproliferation in Sjögren's syndrome, Clin. Exp. Immunol. 9, 199(1971).

90. Gershwin, M.E. and A.D.Steinberg, Loss of suppressor function as a cause of lymphoid malignancy, Lancet 2, 1174(1973).

91. Warner, N.L., Autoimmunity and the pathogenesis of plasma cell tumor induction in NZB inbred and hybrid mice, Immunogenetics 2, 1(1975).

92. Dauphinee, M.J., N.Talal, A.L.Goldstein and A.White, Thymosin corrects the abnormal DNA synthetic response in NZB mouse thymocytes, Proc. Nat. Acad. Sci. USA 71, 2637(1974).

93. Fu, S.M., R.J.Winchester and H.G.Kunkel, Occurrence of surface IgM, IgD and free light chains on human lymphocytes, J. Exptl. Med. 139, 451(1974).

94. Jobin, M.E., J.L.Fahey and Z.Price, Long-term establishment of a human plasmacyte cell line derived from a patient with IgD multiple myeloma, J. Exptl. Med. 140, 494(1974).

95. Takada, A., Y.Takada and J.Minowada, Immunological functions of a human T-lymphoid cell line (MOLT) I. Release of immunosuppressive factors from the mixture of MOLT-4 cells and sheep red blood cells, J. Exptl. Med. 140, 538(1974).

96. Stocker, J.W., J.J.Marchalonis and A.W.Harris, Inhibition of a T-cell-dependent immune response in vitro by thymoma cell immunoglobulin, J. Exptl. Med. 139, 785(1974).

97. Brouet, J.D., G.Flandrin and M.Seligmann, Indications of the thymus-derived nature of the proliferating cells in six patients with Sézary syndrome, New England J. Med. 289, 341(1973).

98. Yoshida, T., R.Edelson, S.Cohen and I.Green, Migration inhibitory activity in serum and cell supernatants in patients with Sézary syndrome, J. Immunol. 114, 915(1975).

99. Broder, S., R.Humphrey, M.Durm, M.Blackman, B.Meade, C.Goldman, W.Strober and T.A.Waldmann, Impaired synthesis of polyclonal (non-paraprotein) immunoglobulins by circulating lymphocytes from patients with multiple myeloma: Role of suppressor cells, New. Eng. J. Med. (in press) 1975.

VI. Systemic Lupus Erythematosus

100. Zingale, S.B., J.C.Sanchez-Avalos, J.A.Andrada, S.G.Stringa and J.A.Manni, Appearence of anticoagulant factors and certain "autoimmune" antibodies following antigenic stimulation with blood group substances in patients with systemic lupus erythematosus, Arth. and Rheum. 6, 581(1963).

101. Baum,J. and M.Ziff, Decreased 19S antibody response to bacterial antigens in systemic lupus erythematosus, J. Clin. Invest. 48, 758(1969).

102. Alarcon-Segóvia, D., R.F.Galbraith, J.E.Maldonado and F.M. Howard, Systemic lupus erythematosus following thymectomy for myasthenia gravis, Lancet 2, 662(1963).

103. Trayanova, T.G., V.V.Sura and G.J.Svet-Moldavsky, Destruction of human cells in tissue culture by lymphocytes from patients with systemic lupus erythematosus, Lancet 1, 452(1966)

104. Podleski, W.K. and U.G.Podleski, Circulating sensitized lymphocytes in systemic lupus erythematosus, Nature 241, 278(1973).

105. Lindsey, E.S. and M.F.A.Woodruff, Infusion of marrow and spleen cells in irradiated NZB/Bl mice: Amelioration of autoimmune disease, Brit. J. Haemat. 14, 255(1968).

106. Kysela, S. and A.D.Steinberg, Increased survival of NZB/W mice given multiple syngeneic young thymus grafts, Clin. Immunol. and Immunopathol. 2, 133(1973).

107. Steinberg, A.D., Pathogenesis of autoimmunity in New Zealand mice V. Loss of thymic suppressor function, Arth. and Rheum. 17, 11(1974).

108. DeHeer, D.H. and T.S.Edgington, Identification of derepressed autoimmunocompetent B lymphoid cells in NZB mice, Clin. Exp. Immunol. 16, 431(1974).

109. Gershwin, M.E., A.Amed, A.D.Steinberg, G.B.Thurman and A.L. Goldstein, Correction of T-cell function by thymosin in New Zealand mice, J. Immunol. 113, 1068(1974).

110. Askanase, P.W., B.J.Hayden and R.K.Gershon, Augmentation of delayed-type hypersensitivity by doses of cyclophosphamide which do not affect antibody responses, J. Exptl. Med. 141, 697(1975)

VII. Autoantibodies can enhance other forms of immune abnormality

111. Stastny, P. and M.Ziff, Antibodies against cell membrane constituents in systemic lupus erythematosus and related diseases I. Cytotoxic effect of serum from patients with systemic lupus erythematosus (SLE) for allogeneic and for autologous lymphocytes, Clin. Exp. Immunol. 8, 543(1971).

112, Lies, R.B., R.P.Messner and R.C.Williams, Jr., Relative T-cell specificity of lymphocytotoxins from patients with systemic lupus erythematosus, Arth. and Rheum. 16, 369(1973).

113. Luria, G.A. and I.V.Domashneva, Antibodies to thymocytes in sera of patients with schizophrenia, Proc. Nat. Acad. Sci. USA 71,235(1974).

114. Horwitz, D.A. and J.B.Cousar, A relationship between impaired cellular immunity, humoral suppression of lymphocyte function and severity of systemic lupus erythematosus, Am. J. Med. 58, 829(1975).

115. Shirai, T. and R.C.Mellors, Natural thymocytotoxic autoantibody and reactive antigen in New Zealand black and other mice, Proc. Nat. Acad. Sci. USA 68, 1412(1971).

116. Gelfand, M.C., L.M.Parker and A.D.Steinberg, Mechanism of allograft rejection in New Zealand mice II. Role of a serum factor, J. Immunol. 113, 1(1974).

117. Williams, R.C.,Jr., R.W.Griffiths, J.D.Emmons and R.C.Field, Naturally occurring human antiglobulins with specificity for γE (IgE), J. Clin. Invest. 51,955(1972).

118. Abdou, N.I., S.R.Casella, N.L.Abdou and I.A.Abrahamsohn, Comparative study of bone marrow and blood B cells in infantile and acquired agammaglobulinemia. Possible role of circulating anti-IgM in pathogenesis, J. Clin. Invest. 52, 2218(1973).

119. Jasin, H.E. and J.D.Smiley, Rheumatoid factors in human disease, in Immunobiology, F.Bach and R.A.Good, eds., Academic Press, New York 1975 (in press).