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CELLULAR IMMUNITY

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I. GENERAL FEATURES OF CELLULAR IMMUNITY

1. Manifestations of cellular immunity:

a. delayed hypersensitivity
b. homograft rejection and the graft-versus-host reaction
c. tumor immunity
d. host resistance against intracellular infections
e. participation in the immune response
f. autoaggression

The *tuberculin skin test* is the best known example of this form of immunity. The reaction of hypersensitivity to tuberculin has been called "delayed" because of its development after 5 or 6 hours with a peak of erythema and induration between 16-48 hours. Microscopically, after an early mobilization of polymorphs, the inflammatory exudate is predominately composed of mononuclear cells.

1. Uhr, J. W. Delayed hypersensitivity. Physiolog. Rev. *46*:359,1966.

2. Turk, J. L. Delayed hypersensitivity. North-Holland Pub. Co., Amsterdam, 1967.

3. Benacerraf, B. and Green, I. Cellular hypersensitivity. Ann. Rev. Med. *20*:141,1969.

2. Antigens that can elicit delayed hypersensitivity

bacterial antigens (M. Tuberc., Salmonella, Brucella, Pfeifferella, Strep, Peneumococcus, Diphtheria)

fungal antigens (Cryptococcus, Blastomyces, Coccidioidomyces, Histoplasma, Chromoblastomyces, Sporotrichosis, Trichophyton, Candida)

protozoa (Leishmania)

viruses (Vaccina, lymphogranuloma venereum, measles, mumps, herpes simples)

insect bites

serum proteins and other simple protein antigens

simple chemical compounds producing contact sensitivity (picryl chloride, dinitro chlorobenzene, dinitro fluorobenzene, penicillin)

4. Mantoux, C. L' intradermal réaction á la tuberculine et son interprétation clinique. Presse Méd. *18*:10,1910.

5. Uhr, J. W., Salvin, S. B. and Pappenheimer, R. M. Delayed hypersensitivity. II. Induction of hypersensitivity in guinea pigs by means of antigen-antibody complexes. J. Exp. Med. *105*:11,1957.

6. Benacerraf, B. and Gell, P. G. H. Studies on hypersensitivity. I. Delayed and arthus type skin reactivity to protein conjugates in guinea pigs. Immunology *2*:53,1959.

7. Salvin, S. B. Immunologic aspects of the mycoses. Progr. in Allergy *7*:213,1963.

8. Schlossman, S. F., Ben-Efraim, S., Yaron, A. and Sober, H. A. Immunochemical studies on the antigenic determinants required to elicit delayed and immediate hypersensitivity reactions. J. Exp. Med. *123*:1083,1966.

9. Lausch, R. N., Suyers, J. S. and Kaufman, H. E. Delayed hypersensitivity to herpes simplex virus in the guinea pig. J. Immunol. *96*:981,1966.

10. Fellner, M. J., Call, E. H., Allyn, B., Baer, R. L. Delayed hypersensitivity to penicillin. JAMA *210*:2061,1969.

3. Delayed hypersensitivity in sites other than the skin, can occur after injection of antigen into the cornea, bladder mucosa, buccal mucosa, synovial membrane, of sensitized individuals:

11. Schlossman, S. and Stetson, C. A. Vascularization of the cornea during delayed hypersensitivity reactions. J. Immunol. *79*:208,1957.

12. Dumonde, D. C. and Glynn, L. E. The production of arthritis in rabbits by an immunological reaction to fibrin. Brit. J. Exp. Path. *43*:373,1962.

13. Coe, J. E. and Feldman, J. D. Extracutaneous delayed hypersensitivity, particularly in the guinea pig bladder. Immunol. *10*:127,1966.

14. Loewi, G. Experimental immune inflammation in the synovial membrane. I. The immunological mechanism. Immunol. *15*: 417,1968.

15. Adams, D., Williamson, J. J. and Solby, A. E. Delayed hyper sensitivity in guinea-pig oral mucosa. J. Pathol. *97*:495,1969.

4. Origin of cells infiltrating delayed hypersensitivity reactions

The majority of the cells that accumulate in lesions of delayed hypersensitivity are not specifically sensitized cells capable of reacting with the antigen.

16. McCluskey, R. T., Benacerraf, B. and McCluskey, J. W. Studies on the specificity of the cellular infiltrate in delayed hypersensitivity reactions. J. Immunol. *90*:466,1963.

Most of the cells that collect in a specific delayed hypersensitivity reaction are macrophages (monocytes) originating in the bone marrow.

17. Lubaroff, D. M. and Waksman, B. H. Bone marrow as a source of cells in reactions of cellular hypersensitivity. I. Passive transfer of tuberculin sensitivity in syngeneic systems. J. Exp. Med. *128*:1425,1968.

18. Lubaroff, D. M. and Waksman, B. H. Bone marrow as a source of cells in reactions of cellular hypersensitivity. II. Identification of allogeneic or hybrid cells by immunofluorescence in passively transferred tuberculin reactions. J. Exp. Med. *128*:1437,1968.

II. IN VITRO METHODS FOR THE STUDY OF CELLULAR IMMUNITY

The development of *in vitro* tests for the study of cellular immunity offers new possibilities for the elucidation of basic mechanisms and for assessment of function in clinical situations.

Tests	*Mediators*
Inhibition of macrophage migration	MIF
Cytotoxicity	Lymphotoxin
Chemotaxis for macrophages	Chemotactic factor
Lymphocyte proliferation	Mitogenic factor
Inhibition of viruses	Interferon
Other methods	

19. *In vitro* methods in cell-mediated immunity. Bloom, B. R. and Glade, P. R., editors. Academic Press, New York, 1971.

1. Inhibition of macrophage migration

Inhibition of growth from explants of tissues from sensitive animals in the presence of tuberculin was first reported by Rich and Lewis in 1932.

20. Rich, A. R. and Lewis, M. R. The nature of allergy in tuberculosis as revealed by tissue culture studies. Bull. Johns Hopkins Hosp. *50*:115,1932.

An ingenious application of this observation using glass capillary tubes from which macrophages are allowed to migrate was devised by George and Vaughn.

21. George, M. and Vaughn, J. H. *In vitro* cell migration as model for delayed hypersensitivity. Proc. Soc. Exp. Biol. Med. *111*:514,1962.

The use of this and similar techniques has led during the past 8 years to the development of a new field of immunology.

22. David, J. R., Al-Askari, S., Lawrence, H. S. and Thomas, L. Delayed hypersensitivity *in vitro*. I. The specificity of inhibition of cell migration by antigens. J. Immunol. *93*:264,1964.

23. David, J. R., Lawrence, H. S. and Thomas, L. Delayed hypersensitivity *in vitro*. II. Effect of sensitive cells on normal cells in the presence of antigen. J. Immunol. *93*:274,1964.

24. David, J. R., Lawrence, H. S. and Thomas, L. Delayed hypersensitivity *in vitro*. III. The specificity of hapten-protein conjugates in the inhibition of cell migration. J. Immunol. *93*:279,1964.

25. Carpenter, R. R. and Brandriss, M. W. *In vitro* studies of cellular hypersensitivity. II. Relationship of delayed hypersensitivity and inhibition of cell migration by picrylated proteins. J. Exp. Med. *120*:1231,1964.

It was discovered that two cells were involved in the *in vitro* models of delayed hypersensitivity: (1) *sensitized lymphocytes* react with the specific antigen producing and releasing into the medium a migration inhibitory factor *(MIF)*: (2) *macrophages* from the same donor or from another are inhibited nonspecifically.

26. Bloom, B. R. and Bennett, B. Mechanism of a reaction *in vitro* associated with delayed-type hypersensitivity. Science *153*:80,1966.

27. David, J. R. Delayed hypersensitivity *in vitro*: its mediation by cell-free substances formed by lymphoid cell-antigen interaction. Proc. Nat. Acad. Sci. *56*: 72,1966.

28. Svejcar, J., Johanovský, J. and Pekárek, J. Studies on the mechanism of delayed type hypersensitivity in tissue cultures. XI. The influence of substances released during the cultivation of lymph node cells from sensitized organism with antigen on the migration activity of normal spleen cells. Z. Immumforsch. *133*:259,1967.

MIF appears to be a glycoprotein separable from other proteins and mediators present in lymphocyte supernatants, but has not yet been obtained in highly purified form.

29. Remold, H. G., Katz, A. B., Haver, E. and David, J. R. Studies on migration inhibitory factor (MIF): recovery of MIF activity after purification by gel filtration and disc electrophoresis. Cellular Immunol. *1*:133,1970

Specific inhibition of senstitzed *human* lymph node cells by tuberculin and hitoplasmin was demonstrated.

30. Thor, D. E. and Dray, S. A correlate of human delayed hypersensitivity: specific inhibition of capillary tube migration of sensitized human lymph node cells by tuberculin and histoplasmin. J. Immunol. *101*:51,1968.

2. Cytotoxicity

Cytotoxicity of lymphoid cells for a variety of target cells can be demonstrated *in vitro*.

31. Perlmann, P. and Holm, G. Cytotoxic effect of lymphoid cells *in vitro*. Adv. Immunol. *11*:117,1969.

This may occur when the lymphocytes are sensitized against antigens present on the target cells such as histocompatibility antigens.

32. Lundgren, G. *In vitro* cytotoxicity by human lymphocytes from individuals immunized against histocompatibility antigens. I. Kinetics and specificity of the reaction. Influence of metabolic inhibitors and anti-lymphocyte serum. Clinc. Exp. Immunol.*6*:661,1970.

In another situation the lymphocyte is sensitized to a soluble antigen and an indifferent target cell is killed.

33. Ruddle, N. H. and Waksman, B. H. Cytotoxicity mediated by soluble antigen and lymphocytes in delayed hypersensitivity. I. Characterization of the phenomenon. J. Exp. Med. *128*:1237,1968.

34. Ruddle, N. H. and Waksman, B. H. Cytotoxicity mediated by soluble antigen and lymphocytes in delayed hypersensitivity. II. Correlation of the *in vitro* response with skin reactivity. J. Exp. Med. *128*:1255,1968.

35. Ruddle, N. H. and Waksman, B. H. Cytotoxicity mediated by soluble antigen and lymphocytes in delayed hypersensitivity. III. Analysis of mechanism. J. Exp. Med. *128*:1267,1968.

A *cytotoxic factor (lymphotoxin)* is produced by sensitized lymphocytes after contact with antigen.

36. Granger, G. A., Shacks, S. J., Williams, T. W. and Kolb, W. P. Lymphocyte *in vitro* cytotoxicity: specific release of lymphotoxin-like materials from tuberc-lin-sensitive lymphoid cells. Nature *221*:1155,1969.

Lymphotoxin is also produced when lymphocytes are stimulated by mitogenic substances such as PHA.

37. Granger, G. A. and Williams, T. W. Lymphocyte cytotoxicity *in vitro*: activation and release of a cytotoxic factor. Nature *218*:1253,1968.

38. Granger, G. A. and Kolb, W. P. Lymphocyte *in vitro* cytotoxicity: mechanisms of immune and non-immune small lymphocyte mediated target L cell destruction. J. Immunol. *101*:111,1968.

39. Williams, T. W. and Granger, G. A. Lymphocyte *in vitro* cytotoxicity: lymphotoxins of several mammalian species. Nature *219*:1076,1968.

40. Kolb, W. P. and Granger, G. A. Lymphocyte *in vitro* cytotoxicity: characterization of human lymphotoxin. Proc. Nat. Acad. Sci. *61*:1250,1968.

3. Chemotaxis for macrophages

Lymphocytes obtained from guinea pigs exhibiting delayed hypersensitivity were stimulated to produce a soluble factor chemotactic for mononuclear macrophages *in vitro*.

41. Ward, P. A., Remold, H. G. and David, J. R. Leukotactic factor produced by sensitized lymphocytes. Science *163*:1079,1969.

Such supernatants were also chemotactic and produced an inflammatory reaction when injected into the skin.

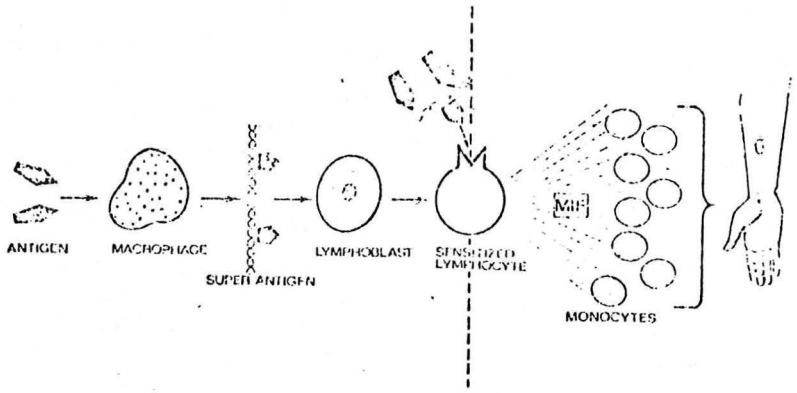
42. Bennett, B. and Bloom, B. R. Reactions *in vivo* and *in vitro* produced by a soluble substance associated with delayed hypersensitivity. Proc. Nat. Acad. Sci. *50*:756,1968.

43. Krejci, J., Pekarek, J., Johanovsky, J. and Svejcar, J. Demonstration of the inflammatory activity of the supernatant of hypersensitive lymph node cells incubated with a high dose of antigen. Immunology *16*:677,1969.

44. Pick, E., Krejci, J. and Turk, J. L. Release of skin reactive factor f-om guinea pig lymphocytes by mitogens. Nature *225*:236,1970.

Similarly they were found to produce inflammation in the synovial membrane.

45. Andreis, M., Ziff, M. and Stastny, P. Experimental arthritis produced by injection of mediators of delayed hypersensitivity. Arthritis and Rheum. *15*:000,1972. (Abs.)



From Quie and Chilgren, Sem. Hematol. *8*:227,1971.

4. Mitogenic effect on lymphocytes

In other work it has been shown that upon stimulation by antigen lymphocytes produce a soluble factor that induces other lymphocytes to transform and divide. This agent amy serve an an amplification mechanism of lymphocyte reactions.

46. Janis, M. and Bach, F. H. Potentiation of *in vitro* lymphocyte reactivity. Nature *225*:238,1970.

47. Maini, R. N., Bryceson, A. D. M., Wolstencroft, R. A. and Dumonde, D. C. Lymphocyte mitogenic factor in man. Nature *224*:43,1969.

48. Falk, R. E., Falk, J. A., Möller E. and Möller, G. Lymphocyte-activating factors released *in vitro* by sensitized and non-sensitized human lymphocytes. Cellular Immunol. *1*:150,1970.

5. Production of interferon, may play a role in host resistance to infection by viruses.

49. Milstone, L. M. and Waksman, B. H. Release of virus inhibitor from tuberculin sensitized peritoneal cells stimulated by antigen. J. Immunol. *105*:1068-1071,1970.

50. Green, J. A., Cooperband, S. R. and Kibrick, S. Immune specific induction of interferon production in cultures of human blood lymphocytes. Science *164*:1415,1969.

6. Other in vitro methods

Macrophages incubated in culture with supernatants of antigen stimulated lymphocytes showed *increased adherence, increased phagocytosis, spreading, motility and hexose monophosphage oxidation* and enhanced killing of bacteria.

51. Mooney, J. J. and Waksman, B. H. Activation of normal rabbit macrophage monolayers by supernatants of antigen stimulated lymphocytes. J. Immunol. *105*:1138-1145,1970.

52. Nathan, C. F., Karnovsky, M. L. and David, J. R. Alterations of macrophage functions by mediators from lymphocytes. J. Exp. Med. *133*:1356,1971.

A *virus plaque assay* based on the observation that antigen activated lymphocytes support growth of RNA viruses has enabled Bloom and coworkers to count antigen sensitive cells. In peripheral blood of tuberculin positive donors they detected an average of 3.6 antigen-sensitive cells per 1000 lymphocytes.

53. Bloom, B. R., Jimenez, L. and Marcus, P. I. A plaque assay for enumerating antigen-sensitive cells in delayed-type hypersensitivity. J. Exp. Med. *132*:16,1970.

54. Jimenez, L., Bloom, B. R., Blume, M. R., and Oettgen, H. T. On the number and nature of antigen-sensitive lymphocytes in the blood of delayed hypersensitive human donors. J. Exp. Med. *133*:740,1971.

III. T CELLS AND B CELLS IN THE MECHANISMS OF IMMUNOLOGIC REACTIONS

1. Heterogeneity of lymphocytes

In the past lymphocytes could be simply classified in three categories: large, medium and small.

Now they are distinguished on the basis of life span, circulating dynamics, "homing" propensities, thymic or bone marrow derivation, cell surface differentiation antigens, buoyant density, ability to recognize antigen, to elaborate antibody, presence of receptors for complement, immunolgical competence, differential sensitivity to immunosuppressive agents, immunoglobulin class produced, anatomic location, etc.

55. Lance, E. M. The heterogeneity of lymphocytes and their interaction. Cellular Immunology *2*:383,1971.

2. Immunologic role of the thymus and the Bursa of Fabricius

Removal of the thymus early in life results in markedly impaired immunologic function.

56. Miller, J. F. A. P. Immunological function of the thymus. Lancet *2*:748,1961.

57. The Thymus in Immunology. Good, R. A. and Gabrielsen, editors. Hoeber-Harper, New York, 1964.

In birds the *thymus* and the *Bursa of Fabricius* control the development of two separate components of the lymphoid system. The thymus component responsible for the functions of *cellular immunity*, the Bursa component in charge of production of *humoral antibodies*.

58. Warner, N. L., Szenberg, A. and Burnet, F. M. The immunological role of different lymphoid organs in the chicken. I. Dissociation of immunological responsiveness. Aust. J. Exp. Biol. Med. Sci. *40*:373,1962.

59. Cooper, M. D., Perey, D. Y., Peterson, R. D. A., Gabriesen, A. E. and Good, R. A. The two-component concept of the lymphoid system *in*: Immunologic deficiency diseases in man. Bergsma, D., editor, Birth Defects Original Article Series, Vol. IV, No. 1, 1968.

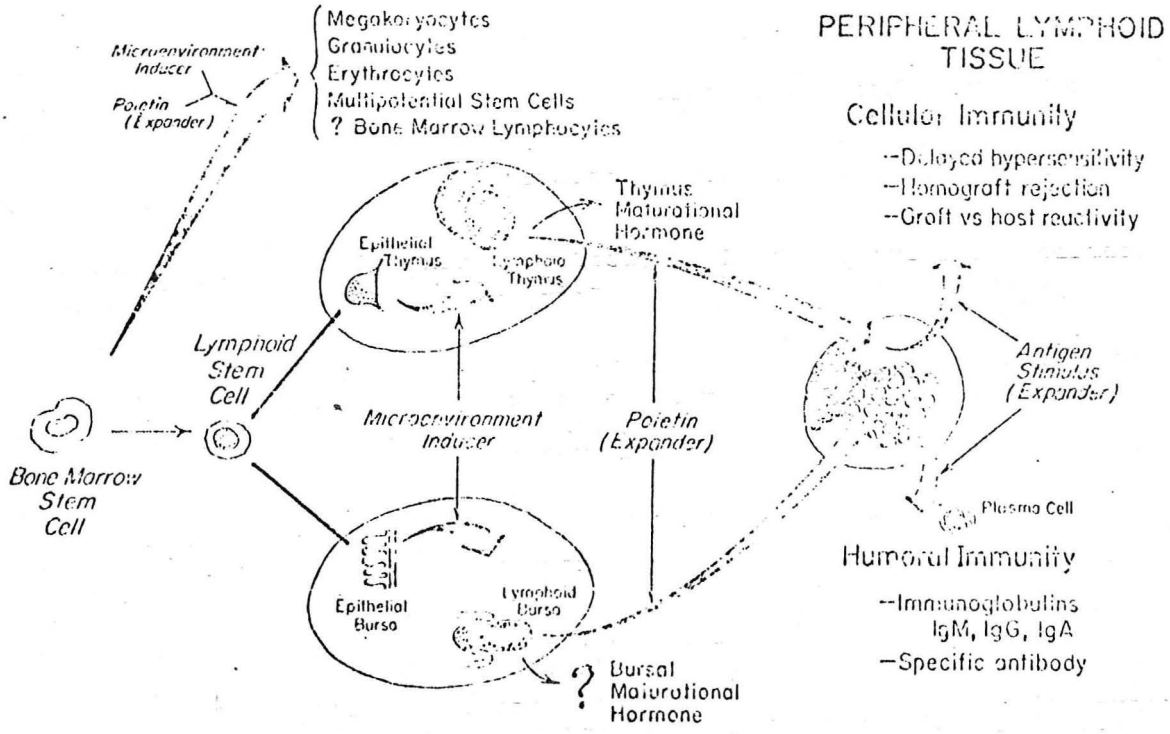
3. T cells and B cells

The bone marrow is a source of *stem cells* of which some differentiate to T cells under the influence of the thymus while others produce B cells via a thymus independent pathway (Bursa or Bursal equivalent). *T cells* are thymus derived and represent the majority of the small lymphocytes of the recirculating pool and those in thymus dependent areas of lymphoid tissue. *B cells* can differentiate, proliferate and mature into *plasma cells* which synthesize humoral antibody. T cells when stimulated by specific antigen can serve several functions: (1) divide to form an expanded population, cellular basis of *immunological memory*, (2) "*killer*" cells for graft target cells, (3) *cooperate during immune response* to certain ("thymus-dependent") antigens by stimulating B cells to produce antibody.

60. Roitt, I. M., Greaves, M. F., Torrigia, G., Brostoff, J. and Playfair, J. H. L. The cellular basis of immunological responses. Lancet *2*:367,1969.

61. Miller, J. F. A. P., Basten, A., Sprent, J. and Cheem, C. Interaction between lymphocytes in immune responses. Cellular Immunol. *2*:469,1971.

62. Thorbecke, G. J. and Mond, J. J. Bone marrow and thymus-derived cell interactions and their relevance to immune tolerance. Ann. N. Y. Acad. Sci. *181*:62,1971.

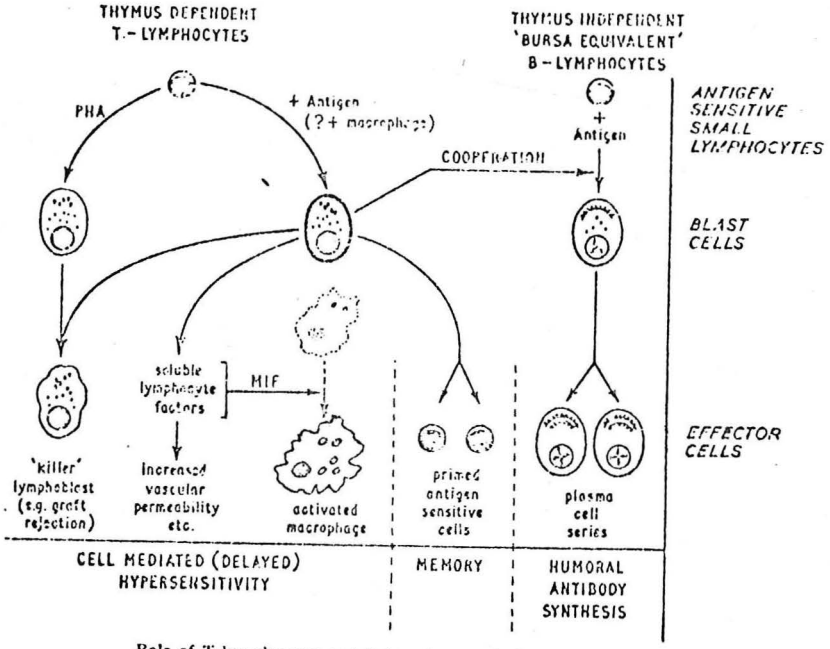


From Immunologic Deficiency Diseases in Man, Bergsma, et al, Editors, Birth Defects Original Article Series, The Nat'l. Fdn. - March of Dimes, p. 18, Vol. IV, No. 1, 1968.

CHARACTERISTICS OF B CELLS AND T CELLS

(from Thorbecke & Mond, 1971)

Property Studied	*B Cells*	*T Cells*
Originate in	Bone marrow, not thymus Bursa of Fabricius (originally also from bone marrow	Thymus (originally from bone marrow)
Differentiate into	Plasma cells, germinal center cells	Recirculating small lymphocytes
Surface Receptors	Immunoglobulin C'	θ and other thymus antigens
Proliferative Response to	Antibody against immunoglobulin; antigens (antibody production)	PHA and other mitogens Histocompatibility antigens Antigens (delayed hypersensitivity)
Role in Immune Response	Humoral antibodies	GVH, graft rejection, delayed hypersensitivity, "helper" function in "thymus dependent" antibody responses



Role of T-lymphocytes and B-lymphocytes in immunological responses.
Many of the events involve active cell proliferation, but for simplicity this has only been indicated at two stages.

From Roitt et al, Lancet *2*:367,1969.

IV. PHYSIOLOGIC ROLE OF CELLULAR IMMUNITY

1. Host defense against intracellular infections

Cellular immunity is involved in resistance to a variety of bacterial, viral, fungal and protozoal infections.

63. Raffel, S. and Ferraresi, R. W. Delayed hypersensitivity in relation to suppression of growth of Listeria monocytogenes by guinea pig macrophages. J. Bact. *100*:635,1969.

64. Collins, F. M. and Mackaness, G. B. The relationship of delayed hypersensitivity to acquired antituberculous immunity. I. Tuberculin sensitivity and resistance to reinfection in BCG-vaccinated mice. Cellular Immunol. *1*:253,1970.

65. Collins, F. M. and Mackaness, G. B. The relationship of delayed hypersensitivity to acquired antituberculous immunity. II. Effect of adjuvant on the allergenicity and immunogenicity of heat-killed tubercle bacilli. Cellular Immunol. *1*:226,1970.

66. Blanden, R. V. Mechanisms of recovery from a generalized viral infection: mousepox. II. Passive transfer of recovery mechanisms with immune lymphoid cells. J. Exp. Med. *133*:1074,1971.

67. Soulsby, E. J. Cell mediated immunity in parasitic infections. J. Parasitol. *56*:534,1970.

As in other forms of cellular immunity resistance to intracellular infections is based on a *cooperation between lymphocytes and macrophages*. When lymphocytes are stimulated by specific antigen macrophages become activated. The *enhanced phagocytosis and mibrobicidal activity* of these cells is then effective against a variety of organisms.

68. Mackaness, G. B. The monocyte in cellular immunity. Sem. Hematology. *7*:172,1970.

Infections are frequent in patients with *impaired cellular immunity due to the use of immunosuppressive drugs*.

69. Folb, P. I. and Trounce, J. R. Immunological aspects of candida infection complicating steroid and immunosuppressive drug therapy. Lancet *2*:112,1970.

70. Reynolds, E. S., Walls, K. W., Pfeiffer, R. I. Generalized toxoplasmosis following renal transplantation. Arch. Int. Med. *118*:401,1966.

71. Montgomerie, J. Z., Bercroft, D. M. O., Croxson, M. C., Dvak, P. B., North, J. D. K. Herpes-simplex-virus infection after renal transplantation. Lancet *2*:867,1969.

72. Stinson, E. B., Bieber, C. P., Griepp, R. B., Clark, D. A., Shumway, N. E., Remington, J. S. Infectious complications after cardiac transplantation in man. Ann. Int. Med. *74*:22,1971.

Similarly in patients with *Hodgkin's disease* disseminated *herpes zoster* was very frequent.

73. Sokal, J. E. and Firat, D. Varicella-Zoster infection in Hodgkin's disease. Am. J. Med. *39*:452,1965.

Impairment of cellular immunity in Hodgkin's disease can be very severe and clearly demonstrable by both *in vivo* and *in vitro* testing.

74. Hersh, E. M. and Oppenheim, J. J. Impaired *in vitro* lymphocyte transformation in Hodgkin's disease. New Engl. J. Med. *273*:1006,1965.

75. Brown, R. S., Haynes, H. A., Foley, H. T., Godwin, H. A., Berard, C. W. and Carbone, P. P. Hodgkin's disease. Immunologic, clinical and histologic features of 50 untreated patients. Ann. Int. Med. *67*:291,1967.

X X X

Case 1. Lymphosarcoma with impaired cellular immunity and multiple infections

N.C. PMH #403770

A 56 year old white woman known to have lymphosarcoma developed generalized herpes zoster of the face, scalp and truck, she was also found to have buccal moniliasis and intermittent fever and compression fractures of the spine. On her final admission she was febrile, somewhat obtunded and had numerous petechiae. Spinal fluid contained 3 polys, 9 lymphs and 65 RBC. Platelet count was 4,500. She developed bloody diarrhea and blood pressure could not be maintained.

At autopsy in addition to malignant lymphocytic lymphoma involving lymph nodes, bone marrow, liver and kidneys it was found that she had: (1) active disemminated herpes zoster involving skin and oral mucosa; (2) candidiasis involving mouth, pharynx, epiglottis, esophagus and stomach; (3) aspergillosis of the lungs; and (4) toxoplasmosis of myocardium and brain.

X X X

Patients with *lepromatous (low resistance) leprosy* exhibit depressed cell-mediated immunity (anergy to skin tests including lepromin, inability to become sensitized by DNCB, poor blastogenic response in lymphocyte cultures and failure to produce MIF). This is associated with widespread dissemination of leprosy bacilli throughout the body. In contrast, patients with *tuberculoid leprosy* have intact cellular responses; their disease is characterized by fewer lesions and sparcity of organisms.

76. Bullock, W. E. Studies of immune mechanisms in leprosy. New Engl. J. Med. *278*:298,1968.

77. Katz, S. I., DeBetz, B. H. and Zaias, N. Production of macrophage inhibitory factor by patients with leprosy. Arch. Derm. *103*:358,1971.

78. Nelson, D. S., Nelson, M., Thurston, J. M., Waters, M. F. R. and Pearson, J. M. H. Phytohaemagglutinin-induced lymphocyte transformation in leprosy. Clin. Exp. Immunol. *9*:33,1971.

It has been suggested that depression of cellular immunity in lepromatous leprosy is associated with *replacement of thymus dependent areas of lymphoid tissue* by reticulohistiocytes.

79. Turk, J. L. and Waters, M. F. R. Immunological basis for depression of cellular immunity and the delayed allergic response in patients with lepromatous leprosy. Lancet *2*:436,1968.

The importance of cellular immune processes in resistance to infection is also illustrated by a patient with nonlymphopenic hypogammaglobulinemia who was found to have adequate resistance to histoplasma capsulatum despite severe deficit in humoral immunity.

80. Biggar, W. D., Menwissen, H. J. and Good, R. A. Successful defense against histoplasma capsulatum in hypogammaglobulinemia. Arch. Int. Med. *128*:585,1971.

2. Immunosurveillance and cancer

The suggestion that cellular immunity was developed during evolution as a mechanism for control of mutant cells was first made by Thomas and subsequently developed by Burnet.

81. Burnet, M. Immunological surveillance. Sydney, 1970.

This concept is based on the prerequisite that most or all neoplastic cells be antigenic to their host.

82. Prehn, R. T. Immunosurveillance, regeneration and oncogenesis. Prog. Exp. Tumor Res. *14*:1,1970.

The list of such tumor specific antigens is indeed impressive.

83. Smith, R. T. Tumor-specific immune mechanisms. New Engl. J. Med. *278*:1207,1968.

In favor of the concept of immunosurveillance the following are also cited:

a) Neoplasia is generally easier to induce in very young or very old animals.

84. Della Porta, G. and Terracini, B. Chemical carcimogenesis in infant animals. Progr. Exp. Tum. Res. *11*:334,1969.

85. Gross, L. Immunological defect in aged population and its relationship to cancer. Cancer *18*:201,1965.

b) There is an increased occurrence of neoplastic disease in patients with immunologic deficiency,

86. Page, A. R., Hausen, A. E. and Good, R. A. Occurrence of leukemia and lymphoma in patients with agammaglobulinemia. Blood *21*:197,1963.

as well as in patients receiving immunosuppressive drugs.

87. Deodhar, S. D., Kuklinga, A. G., Vidt, D. G., Robertson, A. L., Hagard, J. B. Development of reticulum-cell sarcoma at the site of antilymphocyte globulin injection in a patient with renal transplant. New Engl. J. Med.*280*:1104,1969.

88. Walker, D., Gill, T. J., Carson, J. M. Leiomyosarcoma in a renal alograft recipient treated with immunosuppressive drugs. JAMA *215*:2084,1971.

89. Penn, I., Halgrimson, C. G. and Staryl, T. E. De novo malignant tumors in organ transplant recipients. Transpl. Proc. *3*:773,1971.

90. Schneck, S. A. and Penn, I. De novo brain tumours in renal-transplant recipients. Lancet *1*:983,1971.

91. Fahey, J. L. Cancer in the immunosuppressed patient. Ann. Int. Med. *75*:310,1971.

c) A variety of *in vitro* methods have been used successfully to demonstrate cellular immune reactions against tumor specific antigens.

92. Jagarlamoody, S. M., Aust, J. C., Tew, R. H. and McKahn, C. F. *In vitro* detection of cytotoxic cellular immunity against tumor-specific antigens by a radio-isotope technique. Proc. Nat. Acad. Sci. *68*:1346,1971.

93. Hellström, I. Hellström, K. E., Sjögren, H. O. et al. Demonstration of cell-mediated immunity to human neoplasms of various histological types. Int. J. Cancer *7*:1,1971.

94. Bloom, B. R., Bennett, B., Oettgen, H. F., McLean, E. P. and Old, L. J. Demonstration of delayed hypersensitivity to soluble antigens of chemically induced tumors by inhibition of macrophage migration. Proc. Nat. Acad. Sci. *64*:1176,1969.

d) Supernatants of sensitized lymphocytes stimulated by antigen *in vitro* suppressed tumor growth *in vivo*.

95. Bernstein, I. D., Thor, D. E., Abar, B. and Repp, H. J. Tumor immunity: tumor suppression *in vivo* initiated by soluble products of specifically stimulated lymphocytes. Science *172*:729,1971.

e) Patients with cancer who were unable to become sensitized to DNCB were inoperable or developed early recurrence, patients who reacted to DNCB were free of disease 6 months following surgery.

96. Eilber, F. R. and Morton, D. L. Impaired immunologic reactivity and recurrence following cancer surgery. Cancer *25*:362,1970.

3. Rejection of homografts and the graft-versus-host reaction

Cellular immunity also is largely responsible for homograft rejection such as is seen in *kidney transplantation*

97. Russel, P. S. and Monaco, A. P. The biology of tissue transplantation. Little, Brown and Co., Boston, 1965.

and for the graft-versus-host disease a frequently fatal complication in *human bone marrow transplants*.

98. Kruger, G. R. F., Berard, C. W., DeLellis, R. A. et al. Graft-versus-host disease. Morphologic variations and differential diagnosis in 8 cases of HL-A matched bone marrow transplantation. Am. J. Path. *63*:179,1971.

V. AUTOIMMUNE DISEASES AND OTHER FORMS OF AUTOAGGRESSION

The frequent occurrence of *rheumatoid arthritis in patients with agammaglobulinemia* has suggested that cellular immune mechanisms, intact in such patients, might be responsible for the tissue lesions.

99. Good, R. A., Rotstein, J. and Mazzitello, W. F. The silumtaneous occurrence of rheumatoid arthritis and agammaglobulinemia. J. Lab. Clin. Med. *49*:343,1957.

100. Barnett, E. V., Winkelstein, A. and Weinberger, H. J. Agammaglobulinemia with polyarthritis and subcutaneous nodules. Amer. J. Med. *48*:40,1970.

In patients with *polymyositis, lymphocytes were activated by muscle extracts* to take up tritiated thymidine and to become cytotoxic for fetal muscle and other tissues in culture.

101. Currie, S., Saunders, M., Knowles, M. and Brown, A. E. Immunological aspects of polymyositis. The *in vitro* activity of lymphocytes on incubation with muscle antigen and with muscle cultures. Quart. J. Med. *15*:63,1971.

102. Currie, S., Saunders, M., and Knowles, M. Immunological aspects of systemic sclerosis *in vitro*. Activity of lymphocytes from patients with the disorder. Br. J. Dermatol. *84*:400,1971.

103. Johnson, R. L., Fink, C. and Ziff, M. Studies of cytotoxins produced in dermatomyositis (DMS) and polymyositis (PMS). Arthritis and Rheum. *14*:391,1971. (Abst.)

X X X

Case 2. Polymyositis

B.C. PMH #035120

A 42 year old negro female first developed weakness of shoulders, and upper and lower extremities during the summer of 1968. When admitted in November 1968 she had elevated aldolase, CPK and transaminase and the EMG as well as muscle biopsy were consistent with polymyositis. She was treated with high dose steroids (Prednisolone 60mg/d) and developed G.I. bleeding, osteoporosis with compression fracture of lumbar spine and elevation of the blood sugar.

Subsequently she stopped her medications and relapsed. On admission in September 1969, she was very weak. Could not lift head from pillow and arms could be raised only a little. She had marked difficulty swallowing. Her heart was enlarged. Serum aldolase was 16.2, SGOT 264, CPK 586.

Was treated with Prednisolone and Cytoxan with slow improvement over a period of several weeks.

X X X

Cytotoxic effect of lymphocytes and presence of substances associated with cellular immunity have been reported in joint fluids or synovial tissue from patients with *rheumatoid arthritis*.

104. MacLennan, I. C. M. and Loewi, G. The cytotoxic activity of mononuclear cells from joint fluid. Clin. Exp. Immunol. *6*:713,1970.

105. Cawley, M. I. D. and Willoughby, D. A. Lymph-node permeability factor in human synovial tissue as a possible mediator of chronic joint inflammation. Lancet *2*:24,1967.

106. Stastny, P. and Ziff, M. Macrophage migration inhibition and cytotoxicity in acute and chronic inflammation *in*: Immunopathology of Inflammation. Forscher, B. K. and Houck, editors. Excerpta Medica, Amsterdam, 1971, p. 66.

Peripheral lymphocytes from patients with *glomerulonephritis* and anti-glomerular-basement-membrane antibodies were stimulated to produce MIF after incubation with human glomerular-basement-membrane antigen.

107. Rocklin, R. E., Lewis, E. J. and David,J. R. *In vitro* evidence for cellular hypersensitivity to glomerular-basement-membrane antigens in human glomerulonephritis. New Engl. J. Med. *284*:497,1970.

Other similar studies have been performed in the *Buillain-Barre syndrome, multiple sclerosis and idiopathic thrombocytopenia.*

108. Rocklin, R. E., Sheremater, W. A., Feldman, R. G., Kies, M. W., and David, J. R. The Guillain-Barre syndrome and multiple sclerosis *in vitro* cellular responses to nervous-tissue antigens. New Engl. J. Med. *284*:803,1971.

109. Clancy, R. Cellular immunity to autologous platelets and serum-blocking factors in idiopathic thrombocytopenic purpura. Lancet *1*:6,1972.

In slow virus diseases such as *LCM disease* of mice it has been postulated that the basis of the development of lesions is the *"rejection" of virus infected tissue by the host.*

110. Hotchin, J. Virus, cell surface and self. Am J. Clin. Path. *46*:333,1971.

LCM viruses did not injure tissue culture cells but when sensitized lymphocytes were added to such cultures virus infected cells were destroyed, non-infected cells were spared. Indicated that a *cellular immune response specific for virus antigen was injurious to the virus infected cells.*

111. Oldstone, M. B. A., Habel, K. and Dixon, F. J. The pathogenesis of cellular injury associated with persistant LCM viral infection. Fed. Proc.*28*:429,1969.

VI. DEFICIENCY SYNDROMES

Primary specific immunodeficiency results from a failure to produce the effectors of the immune response, i.e., antibodies and sensitized lymphocytes. This excludes hypercatabolic states, deficiency due to exogenous causes (x-ray, cytotoxic drugs), lymphopenia due to intestinal lymphagiectasia, neoplasia, and deficiency associated with complement defects or with phagocytic dysfunction syndrome.

The primary immunodeficiency diseases are best understood in the context of the two-component concept of the lymphoid system and in relation to the problble cellular defects underlying each disorder.

112. Peterson, R. D. A., Cooper, M. D. and Good, R. A. The pathogenesis of immunologic deficiency diseases. Am J. Med. *38*:579,1965.

113. Funderberg, H. H., Good, R. A., Hitzig, W., et al. Classification of the primary immune deficiencies: WHO recommendation. New Engl. J. Med. *283*:656,1970.

CLASSIFICATION OF PRIMARY IMMUNODEFICIENCY DISORDERS

(from Fudenberg, Good, Hitzig et al, New Engl. J. Med., 1970)

Type	*Suggested Cellular Defect*		
	B Cells	*T Cells*	*Stem Cells*
X-linked agammaglobulinemia	+		
Selective Ig deficiency (IgA)	+		
Transient hypogamma of infancy	+		
X-linked immunodeficiency with hyper IgM	+		
Thymic hypoplasia (pharyn. pouch syndrome, Di George		+	
Episodic lymphopenia with lymphocytotoxin		+	
Immunodef. with normal or hyper Ig	+	+	
Immunodef. with ataxia Telangiectasia	+	+	
Immunodef. with thrombocytopenia and eczema	+	+	
Immunodef. with thymoma	+	+	
Immunodef. with short-limbed dwarfism	+	+	
Immunodef. with generalized hematopoietic hypoplasia	+	+	+
Severe combined immunodeficiency (a) autosomal recessive	+	+	+
(b) X-linked	+	+	+
(c) sporadic	+	+	+
Variable immunodeficiency	+	+	

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Case 3. Primary lymphopenic immunologic deficiency

H. O. CMC *

A 7-1/2 month old white male infant was admitted to Children's Medical Center with fever and bilateral bronchopneumonia. He had developed oral and cutaneous moniliasis resistant to therapy since the age of 5 months. His height and weight were normal for his age. He was in moderate respiratory distress and had oral and cutaneous moniliasis. The lung infection worsened in spite of antibiotic therapy and it was found that he had osteomyelitis involving the left proximal humerus, the distal right ulna, left seventh and eighth ribs, and ninth dorsal vertebra. A lung biopsy performed on the 22nd hospital day showed *Pneumocystis carinii* on special stains and subsequently grew *Mycobacterium Kansasii*. The patient's immunoglobulin G and A levels were low. He had a negative Schick test, isohemagglutinins anti-A 1:16, anti-B 1:12. Precipitating antibodies against diphtheria toxoid were present to a dilution of 1:80 and precipitins against atypical mycobacteria including *Myc. Kanasii* were demonstrated. Total peripheral lymphocyte counts were low, tuberculin test negative, candida skin test negative, he failed to become sensitized to DNFB and a very reduced response of his lymphocytes to PHA was observed. A skin allograft was not rejected.

The patient developed progressive respiratory distress and died on the 28th day. At autopsy the lungs showed *Pneumocystis carinii* and *Myc. Kansasii*. The latter was also present in necrotic foci in the thymus, appendix, and spleen. There were multiple areas of osteomyelitis. Lymphoid tissue was very deficient. No tonsils, lymph nodes or Peyer's patches were found. The thymus was very small and had no Hassal's corpuscles.

*McCracken, G. H. and Reynolds, R. C., Am. J. Dis. Child. *120*:143,1970.

X X X

The relationship between immunodefiency and infection is complex, since each may lead to the other. An interesting situation where this question remains unresolved is given by the patients with

Chronic Mucocutaneous Candidiasis with impaired delayed hypersensitivity. Patients with this syndrome have generalized *cutaneous anergy*, they fail to become sensitized to DNCB. *In vitro* their lymphocytes can be stimulated by *PHA* or *Candida* antigen to blast cell formation however they *fail to produce MIF*.

114. Chilgren, R. A., Quie, P. G., Menwissen, H. J. and Hong, R. Chronic mucocutaneous candidiasis, deficiency of delayed hypersensitivity, and selective local antibody defect. Lancet *2*:688,1967.

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

116. Chilgren, R. A., Menwissen, H. J., Quie, P. G., Good, R. A., and Hong, R. The cellular immune defect in chronic mucocutaneous candidiasis. Lancet *1*:1286,1969.

117. Canales, L., Middlemas, R. D., Lonio, J. M., and South, M. A. Immunological observations in chronic mucocutaneous candidiasis. Lancet *2*:567,1969.

118. Kirkpatrick, C. H., Chandler, J. W. and Schimke, R. N. Chronic mucocutaneous moniliasis with impaired delayed hypersensitivity. Clin. Exp. Immunol. *6*:375,1970.

119. Kirkpatrick, C. H., Rich, R. R., Bennett, J. E. Chronic mucocutaneous candidiasis: model-building in cellular immunity. Ann. Int. Med. *74*:955,1971.

VII. CLINICAL TESTS FOR ASSESSING IMMUNE FUNCTION IN PATIENTS WITH IMMUNODEFICIENCY SYNDROMES

120. Fudenberg, H., Good, R. A., Goodman, H. C., et al. Primary immunodeficiencies. Report of a World Health Organization Committee. Pediatrics *47*:927,1971.

1. *Measurement of serum immunoglobulin concentrations* by the single radial diffusion assay of Mancini. WHO now makes available reference preparations for the five classes of immunoglobulins. Electrophoresis and/or immunoelectrophoresis may be used as a preliminary screening procedure.

   IgG, less than 200 mg/100 ml significant if associated with symptoms

   IgA, may be undetectable in 0.1% of the normal population

2. *Assessment of antibody formation following immunization*

   a. *Natural antibodies*: A and B isohemagglutinins, heteroagglutinins against sheep or rabbit RBC, antistreptolysin, anti-E. coli.

b. *Routine active immunization*: diphtheria, pertusis, tetanus. Give DPT 0.5 ml i.m. for 3 successive weeks. Blood is taken 14 days after last injection. Antibodies determined by hemagglutination.

c. *Other active immunization:*

Killed polio vaccines 1.0 ml i.m. at 2 week intervals for 3 doses. Blood taken 2 weeks after last injection. Antibody determined by virus neutralization.

Pneumococcal polysaccharide 0.1 mg i.m. for 3 successive weekly injections. Blood taken 2 weeks after last injection. Antibody estimated by precipitin or antigen-binding technique.

H. influenza polysaccharide 0.05 mg subcutaneous. Blood taken 2 weeks later. Hemagglutination or antigen binding.

N. Meningitides polysaccharide 0.05 mg subcutaneous. Blood taken 2 weeks later. Antibody determined by preciptin.

Vi antigen from E. Coli 100 µg subcutaneous in 1.0 ml saline. Two weeks later antibody determined by hemagglutination.

Flagellin 5 µg in 0.1 ml of phosphate buffered saline, pH 7.0, subcutaneous.

3. *Assessment of cell-mediated immunity*

a. *Pre-existing immunity*
For skin testing, intradermally:

Purified protein derivative (PPD) 0.1 ml first strength; if negative repeat with second strength.

Candida 0.1 ml of a 1:10 dilution for infants or of a 1:100 dilution for older children and adults

Trichophytin, as for Candida

Streptococcal antigens, 0.1 ml Streptokinase-streptodornase at a concentration of 5 units per 0.1 ml. If negative repeat at a concentration of 40 per 0.1 ml.

Mumps skin test antigen 0.1 ml.

Reactions should be read at 4 hours to assess any Arthus reactions and at 24 and 48 hours for delayed hypersensitivity. Diameter of induration and erythema should be recorded.

b. Active sensitization

2,4-dinitrochlorobenzene (DNCB) in acetone, (30% for adults, 10% for infants) 0.05 ml is applied to the volar surface of the forearm on a filter paper 1 cm in diameter. A test dose is applied at the same time to serve as presensitization control. The filter papers are removed after 12 to 24 hours and the control read 48 hours after application.

Testing of sensitivity is performed 14 to 21 days later with 0.05 ml of a 0.1% or 0.05% solution of DNCB in acetone on a filter paper. Paper removed 12-24 hours later and reaction assessed 48 hours after application. Subjects who remain negative should be skin tested again 30 to 35 days after attempted sensitization.

Skin reactions are read as follows:
no reaction = 0; erythema only = 1+; erythema and induration = 2+; vesiculation = 3+; bullae and ulceration = 4+. Only 2+ or greater are taken as evidence of sensitization.

c. Lymphocyte transformation

Stimulation by antigens, allogeneic lymphocytes and mitogens such as phytohemagglutinia (PHA). Results evaluated by morphologic change, incorporation of H3-thymidine measured by scintillation counting or by autoradiography.

Reference 19.

d. Assay for production of mediators of delayed hypersensitivity

MIF is the best studied.
The method of choice at present consists of culturing blood lymphocytes with antigen for periods up to 3 days and in a second stage addition of the concentrated cell-free supernatant to chambers containing guinea pig macrophages.

121. Thor, D. E., Jureziz, R. E., Veach, S. R., Miller, E. and Dray, S. Cell migration inhibition factor released by antigen from human peripheral lymphocytes. Nature *219*: 755,1968.

122. Rocklin, R. E., Meyers, O. L. and David, J. E. An *in vitro* assay for cellular hypersensitivity in man. J. Immunol. *104*:95,1970.

A method of direct human leukocyte migration inhibition although more convenient has not been generally accepted as a concomitant of cell-mediated immunity.

123. Bendixen, G. and Soborg, M. A leucocyte migration technique for *in vitro* detection of cellular (delayed type) hypersensitivity in man. Danish Med. Bull. *16*:1,1969.

The importance of *in vitro* methods in cell mediated immunity is only now being recognized and will certainly lead to other developments.

124. Bloom, B. R. *In vitro* methods in cell-mediated immunity in man. New Engl. J. Med. *284*:1212,1971.

125. Lockshin, M. D. and Bombardeiri, S. *In vitro* delayed hypersensitivity in normal and hyporeactive patients. Immunol. *20*:641,1971.

VIII. THERAPY

1. Reconstitution by homografts

Patients with severe combined immunodeficiency have been completely corrected by *bone marrow transplantation.*

126. Meuwissen, H. J., Gatti, R. A., Terasaki, P. I., Hong, R. and Good, R. A. Treatment of lymphopenic hypogammaglobulinemia and bone marrow aplasia by transplantation of allogeneic marrow. Crucial role of histocompatibility matching. New Engl. J. Med. *281*:691,1969.

127. De Koning, J., Dooren, L. J., Van Bekkum, D. W., van Rood, J. J., Dicke, K. A., Ridl, J. Transplantation of bone marrow cells and fetal thymus in an infant with lymphopenic immunological deficiency. Lancet *1*:1223,1969.

128. Amman, A. J., Meuwissen, H. J., Good, R. A., and Hong, R. Successful bone marrow transplantation in a patient with humoral and cellular immunity deficiency. Clin. Exp. Immunol. *7*:343,1970.

Fetal thymus grafts have reconstituted thymus-dependent immune functions in children with *thymic aplasia* (Di George's Syndrome). With recovery of cellular-immune faculties, however, the grafter thymus is rejected.

129. August, C. S., Levey, R. H., Berkel, A. I., and Rosen, F. S. Establishment of immunological competence in a child with congenital thymic aplasia by a graft of fetal thymus. Lancet *1*:1080,1970.

2. *Transfer factor*

Cell-free extracts of circulating lymphocytes were found to convey a state of sensitivity to previously unresponsive human subjects. The active material in these extracts was called *transfer factor*.

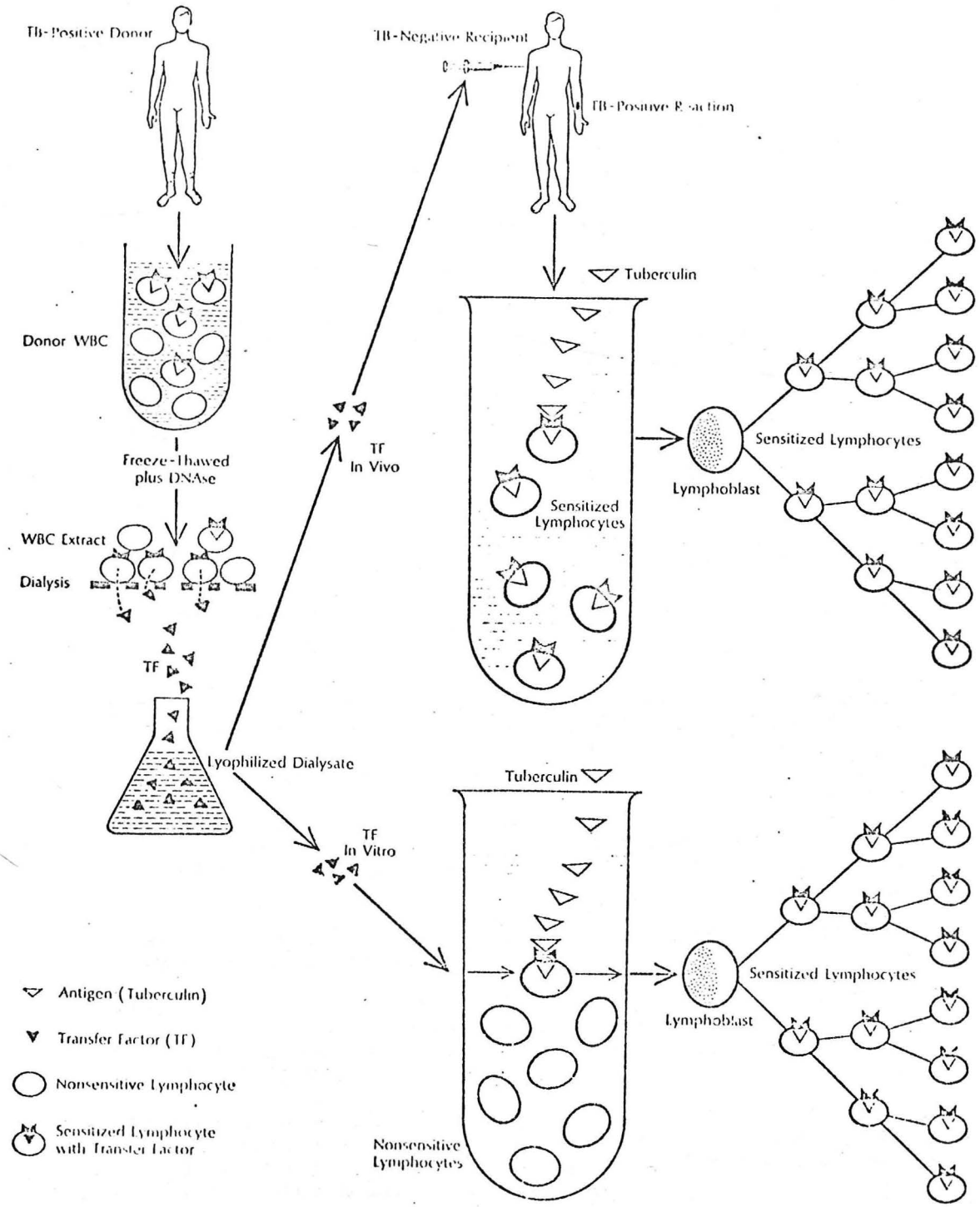
130. Lawrence, H. S. Transfer factor. Advances Immunol. *11*:195-266,1969.

131. Lawrence, H. S. and Valentine, F. T. Transfer factor and other mediators of cellular immunity. Am. J. Path. *60*:437,1970.

Transfer factor was found to be a dialyzable moiety of less than 10,000 molecular weight, capable of inducing in the recipient specific delayed hypersensitivity present in the donor. It did not transfer the capacity to form antibodies, it was not antigenic nor an immunoglobulin fragment. Sensitivity transferred was systemic and lasted months or 1 to 2 years.

132. Baram, P. and Mosko, M. M. A dialysable fraction from tuberculin-sensitive human white blood cells capable of inducing tuberculin-delayed hypersensitivity in negative recipients. Immunology *8*:461,1965.

133. Lawrence, H. S. Transfer factor and cellular immune deficiency disease. New Engl. J. Med. *283*:411,1970.



From Lawrence, Hosp. Prac., Dec. 1969.

Use of *transfer of delayed hypersensitivity* with leukocytes to treat patients with certain kinds of uncontrollable infections is now well documented.

This includes a child with *disseminated vaccinia*.

134. Kempe, C. H. Studies on smallpox and complications of smallpox vaccination. Pediatrics *26*:176,1960.

A similar case in an adult where high levels of antibody against vaccinia virus were demonstrated and administration of immune globulin failed to stop the disease.

135. O'Connell, C. J., Karzon, D. T., Barron, A. L., Plant, M. E. and Ali, V. M. Progressive vaccinia with normal antibodies. Ann. Int. Med. *60*:282,1964.

Use of *dialyzable transfer factor* has also been successful in *chronic mucocutaneous moniliasis*. It has the advantage that there is no hazard of graft-versus-host reaction or of hepatitis.

136. Buckley, R. H., Lucas, Z. J., Hatlter, B. G., Zmijenski, C. M., and Amos, D. B. Defective cellular immunity associated with chronic mucocutaneous moniliasis and recurrent staphylococcal batryomycosis: immunological reconstitution by allogenic bone marrow. Clin. Exp. Immunol. *3*:153,1968.

137. Rocklin, R. E., Chilgren, R. A., Hong, R. and David, J. R. Transfer of cellular hypersensitivity in chronic mucocutaneous candidiasis, monitorea *in vivo* and *in vitro* Cell. Immun. *1*:290,1970.

138. Swanson, R. and Pabst, H. Successful therapy with transfer factor (T.F.) in mucocutaneous candidiasis. Clin. Res. *20*:269,1972 (Abs.)

In addition to disseminated candidiasis it has been used in some cellular immune deficiency states.

139. Levin, A. S., Stities, D. P., Spitler, L. E. et al. Induction of delayed hypersensitivit- in a Wiscott-Aldrich patient by transfer factor. Clin Res. *18*:428,1970.

140. Levin, A. S., Spitler, L. F., Stites, D. P. A genetically determined cellular immune deficiency: clinical and laboratory response to therapy with "transfer factor". Proc. Nat. Acad. Sci. *67*:821,1970.

Its use has been suggested for the *conversion of leprosy* from the lepromatous to the tuberculoid form.

141. Transfer factor and leprosy. (Editorial) New Engl. J. Med. *278*:333,1968.

The transfer of cutaneous sensitivity to lepromin and tuberculin has already been reported.

142. Bonaparte, Y., Morgenfeld, M. C., Paradisi, E. R. Immunology of leprosy. New Engl. J. Med. *279*:49,1968.

The possibility of using specific transfer factor to *stimulate tumor immunity* and cause the rejection of neoplasms as if they were homografts was also considered.

Reference 129.