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SPECIAL ARTICLE

Tuberculosis and Immunology#

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In 1801 Edward Jenner[1] published his celebrated monograph entitled "An inquiry into the Causes and Effects of the Variolae Vaccinae" which noted the first authentic observation that infection could modify the body in such a manner that a subsequent contact of the infecting agent with the tissue would produce a more rapid local reaction than that which occurred as a result of the previous contact. The process is known nowadays as the "phenomenon of hypersensitivity". Ninety years later (1891) Robert Koch[2] made a similar observation during his experiments on tuberculous reinfection, which became the starting point of modern tuberculosis immunology.

In earlier days, the focus of interest was primarily on immunologic defense mechanisms. Attempting to isolate an antigen to serve as the basis of a vaccine, Rober Koch[3] prepared crude extracts of cultures of the tubercle bacilli, called "tuberculin", but the material never fulfilled Koch's ambition for a vaccine; nevertheless, it led to an important means (Mantoux test) for determining the state of "tuberculin-type" or "delayed-type" hypersensitivity in individuals formerly exposed to the organism. Thereafter, the scope and character of tuberculosis immunology changed vastly. In recent years there have been dramatic developments in many different areas, sparked by the advances in molecular biology, hybridoma technology, and T-cell cloning.

This review will provide an update on selected areas of the delayed-type hypersensitivity relevant to the understanding of its induction, reactivity and mechanisms of anergy.

Definition

Delayed-type hypersensitivity (DTH) denotes a state of altered reactivity of the host to a variety of antigenic substances, especially those derived from infective organisms; an exception is the case of simple chemicals in contact hypersensitivity. DTH is an *in vivo* manifestation of the activity of a specialized subset of T cells.

Induction

Definitive evidence that special lymphocytes were responsible for a form of delayed-type hypersensitivity was first provided by Lansteiner and Chase.[4] Thereafter appeared a great number of published works on this particular subject which provide advanced understanding of the cellular as well as the biochemical basis of the mechanisms involved. A simplistic version of the sequence of events in the induction of DTH[5,6] is illustrated in Figure 1. The immunological process starts when macrophages phagocytize organisms and present the antigens to T-lymphocytes. Only lymphocytes with highly specific receptors will recognize the antigens in the context of HLA-DR glycoproteins on the macrophage membranes. In other words, the lymphocyte must respond to two signals, antigen and HLA-DR, simultaneously. Early events in the activation of T cells include expression of receptors for IL-2 on the T-cell surface. In order for full activation to occur, the process of induction requires synthesis and release of interleukin-1

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(IL-1), a soluble cytokine, from macrophages. IL-1 stimulates T cells to produce interleukin-2 (IL-2); the fit of IL-2 in its corresponding receptor on T cells then leads to clonal expansion of activated, specifically sensitized T-cells. Activated T-cells liberate soluble factors (lymphokines) especially gamma interferon (IFN-γ) to promote activity and differentiation of macrophages, and continue to activate antigen-presenting cells, which in turn activate additional T-cells. Induction of delayed-type hypersensitivity becomes established in the presence of activated helper T-cells (T_{DH} cells). A concomitant feature of DTH induction is a blastogenic response of cells in the paracortical (T-cell-dependent) area of lymph nodes draining the areas of sensitization.[7] From there, DTH can be transferred passively to non-infected persons by those immune lymphoid cells. The success of DTH transfer by subcellular entities ("transfer factor of Lawrence"[8] or other serum factors[9-11]) has not been achieved in a reproducible manner.

The time required for the appearance of hypersensitivity (based on cutaneous reactivity) following a primary tuberculous infection depends upon a number of factors.[12]

(1) The number of bacilli that enter the tissues The quantitative relationship has been demonstrated. In the guinea pig,[13] after infection with large doses of virulent bacilli, cutaneous hypersensitivity appears in the latter part of the first week, and may be as early as the third day; when infected with small doses, many weeks may pass before DTH can be demonstrated. For humans, available data have been obtained from disastrous events involving the Luebeck infants,[14] who were infected accidentally during the first days of life; the earliest detected hypersensitivity was seen on the 23rd day following the administration of the bacilli. The appearance of DTH has also been observed between 3 and 13 weeks following the injection of killed tubercle bacilli into infants and young children.[15]

(2) The virulence of the bacilli The more virulent the strain, the more rapidly and effectively will hypersensitivity become established.

(3) The native resistance of the host Differences in the native resistance of different hosts can exert a marked effect upon the rate of development of hypersensitivity. The more susceptible the host, the sooner will the bacilli multiply, and the more rapidly and effectively will DTH be established.

(4) The inherent capacity of the host to develop DTH Inherent capacity is determined by the basic, constitutional make-up of the individual, and by the temporary physiological or pathological state of the individual at the time when the body is called upon to develop DTH. For instance, Negroes tend to develop a higher degree of DTH and hence react more intensely to tuberculin than do Caucasians.[16] Certain conditions are known factors that lower resistance to tuberculosis (i.e. genetic pedigree, stress, infancy and old age, intercurrent viral infections, malnutrition, diabetes mellitus, silicosis) will, if present at the time of infection, permit a more rapid multiplication of bacilli and consequently increase the rapidity with which DTH becomes established.[17]

(5) The route by which the bacilli enter the body The difference in the sensitizing efficacy of different routes of infection is not clearly understood. Results from animal experiments[17] revealed that the intravascular route is a much less effective

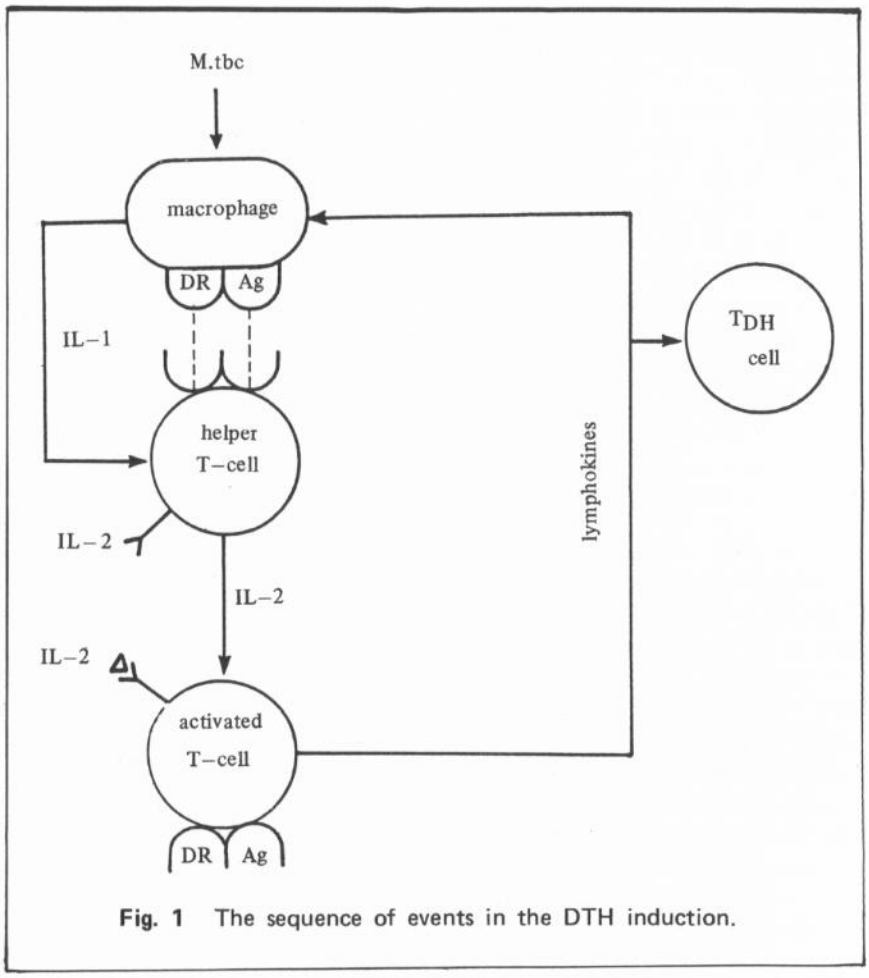

Fig. 1 The sequence of events in the DTH induction.

pathway for the establishment of DTH than is intraperitoneal, intratesticular, intracutaneous, or subcutaneous injection. Intravenous injection of the antigen is, on the other hand, the most efficacious method of desensitization.

Delayed-type hypersensitivity reactions

Shortly after infection with the tubercle bacillus has been established, hypersensitivity makes its appearance, i.e. the tissues of the hypersensitive body will be locally reactive by amounts of the protein that are harmless to the non-infected body. This is a T-cell-dependent immune phenomenon manifested by an inflammatory reaction at the site of antigen deposition that reaches its peak intensity 24-48 hours after initiation. These characteristics can be elicited by skin testing with antigens, e.g. tuberculin or chemically reactive compounds such as trinitrochlorobenzene (TNCB) or dinitrofluorobenzene (DNFB). A variety of *in vitro* tests, e.g. T-cell proliferation assay, and the production and assay of lymphokines such as migration inhibition factor (MIF), is also available.

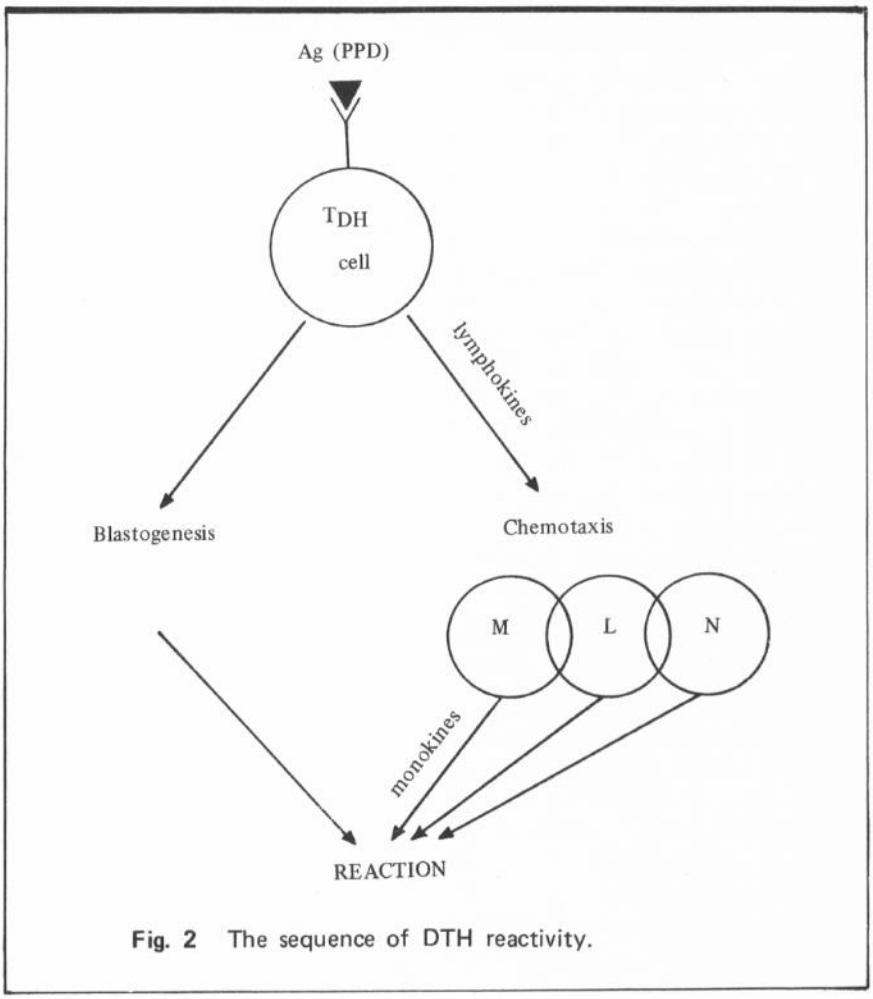

Fig. 2 The sequence of DTH reactivity.

The course of DTH reaction can be summarized in the following sequences (Figure 2).[18] The event starts as immune lymphocytes mediating DTH (T_{DH} cells) encounter antigen at or close to the site of antigen deposition. The specific recognition of antigen results in the activation and proliferation of these cells and the subsequent production of antigen-specific factors, non-specific factors and lymphokines. Some lymphokines are capable of chemotaxising other cell types to the vicinity of the antigen and activating them. These newly attracted cells include monocyte-macrophage lineage as well as other mononuclear cells and neutrophils. Stromal edema occurs only slightly since the DTH reaction does not result in a significant increase in vascular permeability; this process accounts for the indurated, as opposed to erythematous, character of the lesions.

Monocytes and macrophages[19,20] are integral to this immune response; selective migration of monocyte/macrophages appears to be a prominent feature in the reaction due to antigens derived from the causative organisms. At the site of inflammation, they will be activated by the appropriate interactions with antigen, specific immune lymphocytes and lymphokines. Consequently, they may cause non-specific tissue destruction and swelling either directly or through the release of their own monokines.[21] The persistent presence of antigen leads to the development of granulomatous lesions, composed predominantly of mononuclear cells that arise after chronic stimulation of T_{DH} cells.[22] Lymphokines activate connective tissue cells, contributing to the walling of infection and the development of scar tissue.[23]

Anergy in tuberculosis

Hyporesponsiveness to mycobacterial antigens in tuberculosis is of considerable interest. Negative cutaneous tuberculin reactions, besides those caused by improper testing and those secondary to certain diseases (Hodgkin's lymphoma, sarcoidosis, certain malignant neoplasms[24]), drugs (corticosteroids,[25] rifampicin[26,27]), vaccinations and constitutional factors, occur with a highly variable frequency in a wide variety of tuberculous infections and disease,[28-32] and occasionally

for no apparent reason.[28] Likewise, it has been observed from *in vitro* studies that PPD- or mitogen-induced blastogenic responses[26,33-36] as well as the production of IFN-γ[37] and IL-2[38,39] from peripheral blood mononuclear cells (PBMC) from tuberculosis patients are lower than those from healthy subjects. This hypoergic state in tuberculosis patients is seen mostly in slightly older individuals, who are more acutely ill, or have radiographic evidence of more active, more acute disease,[6] or advanced refractory disease.[39] The phenomenon of anergy (more correctly termed suppressed hypersensitivity) frequently disappears as the disease is treated or subsides.[30,32,40-42]

Possible mechanisms of anergy have been attributed to the following:

(1) Defects in chemotaxis prevent active sensitized cells in the circulation (which are capable of responding to antigens) from reaching the site of the skin test. Defective monocyte chemotaxis has been demonstrated in patients with active tuberculosis.[43] The basis for such abnormality is not yet known; somehow the antigen-specific defects in mononuclear cell production of the pivotal molecule IL-2 in such patients may play an integral role.[38]

(2) Immunologic compartmentalization of tuberculin-reactive T lymphocytes owing to migration of reactive cells into areas of active inflammation,[42,44,45] which may lead to a relative depletion of such cells in the blood. However, such sequestration of cells at local lesions does not always cause depletion of circulating tuberculin-sensitive lymphocytes.[46,47] Furthermore, it has been reported that reduction of circulating activated helper T cells (T4-lymphopenia),[48,49] as well as *in vitro* lymphoblastic activity[47,50] were unrelated to the size of cutaneous tuberculin reactions.

In the case of tuberculous pleurisy with effusion, the number of T lymphocytes is significantly higher in pleural fluid than in peripheral blood, and the response of pleural fluid lymphocytes to tuberculin PPD (i.e. blast transformation, immune interferon production) exceeds that of blood mononuclear cells;[46,51-54] this is evidently due to *in situ* expansion of tuberculin reactive lymphocytes[48] together with selective compartmentalization of suppressor cells in the blood.[51] Therefore, sequestration of cells at local sites is not important in anergy.

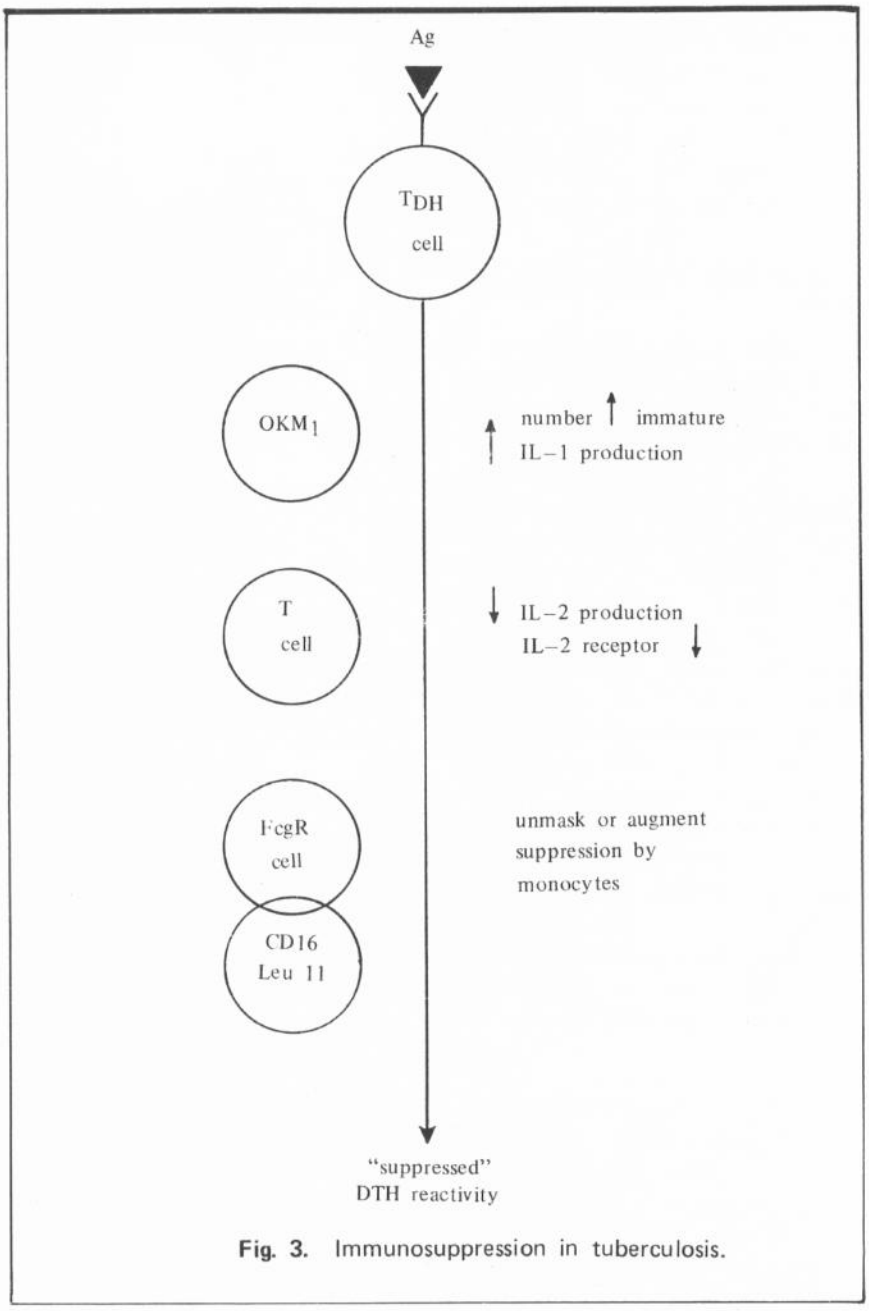

Fig. 3. Immunosuppression in tuberculosis.

(3) Active immunosuppression by circulating T cells and monocytes Although antigen-reactive T lymphocytes capable of expressing DTH to tuberculin antigen are present in the circulation, their activity is masked or suppressed by active immunoregulatory mechanisms[55] via an interesting relationship between suppression by monocytes (adherent mononuclear cells -OKM1-reactive, E-rosette negative[6]) and suppression by T cells.[56] On the one hand, mono-

cytes from patients with tuberculosis differ, both quantitatively and qualitatively, from monocytes from healthy controls,[6] i.e. they are more numerous (owing to premature release from the bone marrow[57]), become activated to be potent suppressors of T-cell generation of IL-2 and blastogenesis in response to PPD,[36] produce more IL-1[36] (a cytokine marker of activation at one time and at other times a part of the mechanism of immunosuppression), and have abnormally regulated HLA-DR expression.[58] A subset of T lymphocytes (T gamma cells) identified by surface receptors for the Fc fragment of IgG (FcγR-positive cells), not only increase in number- as is the case with monocytes- but also they become activated to function as antigen-specific suppressor cells.[56] In this context, the failure of circulating lymphocytes to generate IL-2 in response to PPD stimulation and the presence of partly impaired IL-2 receptor expression on the surface of T cells[38,39] are likely the most important mechanisms. More recent studies have provided additional data that in tuberculosis patients the population of CD16-positive lymphocytes [$Fc\gamma R^+$ non-B cell lymphocytes which are CD-3 (pan-T cell antigen) negative and express CD16 (Leu 11 reactive) antigen] is expanded; these cells contribute to monocyte-mediated suppression of tuberculin-induced generation of IL-2 by T cells.[59]

Although most of the aforementioned data came from *in vitro* studies, similar *in vivo* exposure may contribute to the cell-mediated suppression of lymphocyte responses in hypoergic tuberculosis patients as well.

In brief, the mechanisms of immunosuppression in tuberculosis (Figure 3) involve aberrant surface expression of the HLA-DR gene product on adherent mononuclear cells and abnormalities in immune induction (due to matched antigen-specific defects in production and response to IL-2) and the cytokine cascade (excessive production of IL-1 by monocytes).

(4) Plasma inhibitors of mycobacterial origin (viz. mycobacterial cell wall polysaccharide D-arabino-D-galactan circulating alone or bound in immune complexes) may contribute to the suppression of lymphocyte responses in tuberculosis by a direct inhibitory action on T-lymphocytes and by inducing monocyte proliferation and production of immunoreactive prostaglandin E2 (PGE2).[60] PGE2 has long been known to be a mediator able to suppress immune responses[61] and lymphokine production.[62]

In conclusion, a consistent accumulation of recent experimental evidence clearly shows that a consequence of the immune response elicited by *Mycobacterium tuberculosis* is that the individual eventually becomes susceptible to tuberculous antigens, owing to the state of delayed-type hypersensitivity induced by a specialized subset of T lymphocytes and adherent mononuclear cells. DTH reaction that occur in response to subsequent antigen exposures involve activation and proliferation of local immune lymphocytes, mediating DTH with their provision of mediators capable of chemotaxis attracting other cell types from the circulation and activating them. Monocytes/macrophages are integral to the latter part of the reactivity.

The phenomenon of "anergy" in tuberculosis, with current understanding of its mechanisms, would be better substituted by the term "suppressed hypersensitivity". The event develops as a result of conjoining active immunoregulatory functions of circulating monocytes and T cells during certain stages of active tuberculosis. Exaggerated production of IL-1 by monocytes and low IL-2 production by activated mononuclear cells are key features of the immunosuppression. The basis of the disordered production, however, is not fully understood.

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References

1. Jenner E. An inquiry into the causes and effects of the Variolae Vaccinae. London : LAW, (1798) 1801 : 13.
2. Koch R.Fortsetzung der Mittheilung ueber ein Heilmittel gegen Tuberkulose. Deutsch Med Wschr 1891; 17 : 101-2.
3. Koch R. Weitere Mittheilung ein Heilmittel gegen Tuberkulose. Dtsch Med Wochenschr 1890;16 : 1029-32.
4. Lansteiner K, Chase MW. Experiments on transfer of cutaneous sensitivity to simple chemical compounds. Proc Soc Biol NY 1942; 49 : 688-90.
5. Edwards D, Kirkpatrick CH. The immunology of mycobacterial diseases. Am Rev Respir Dis 1986; 134 : 1062-71.
6. Ellner JJ. Immune dysregulation in human tuberculosis. J Lab Clin Med 1986; 108 : 142-9.
7. Crowle AJ. Delayed hypersensitivity in the mouse. Adv Immunol 1975; 20 : 197-264.
8. Lawrence HS. Transfer factor. Adv Immunol 1969; 11 : 195-266.
9. Bovornkitti S, Kangsadal P, Limpanichakarn S, Indaniyom C. Serum transfer of delayed cutaneous hypersensitivity to tuberculin in man. Dis Chest 1963; 43 : 393-6.
10. Bovornkitti S, Suwanik R, Bhadrakom S, Chulsmaya M, Chantarakul N, Indaniyom C. Passive transfer of delayed

hypersensitivity with Iodine^{131}-labeled serum. Jap J Tuberc 1963; 11 : 28-35.

11. Bhadrakom S, Bovornkitti S, Chulsmaya M, Panpat P. The transfer of delayed cutaneous ractivity to tuberculin with serum protein fractions. Siriraj Hosp Gaz 1963; 15 : 597-9.
12. Rich AR. The pathogenesis of tuberculosis. 2nd Ed. Springfield, IL: Charles C Thomas, 1951 : 351.
13. Hamburger F, Tyoyofugu T. Ueber das zeitliche Auftreten der Tuberkulinempfindlichkeit. Beit z Klin d Tuberk 1910; 17 : 237.
14. Die Sauglingstuberkulose in Luebeck. Arbeit ad Reichsgensdhtsamte, 1935 : 69.
15. Goodwin TC, Schwentker FF. Protective inoculation against tuberculosis in infants by the use of heated killed human tubercle bacilli. J Pediatr 1934; 5 : 475-83.
16. Aronson JD. Incidence of tuberculous infection in some communities of the south. Am J Hyg 1931; 14 : 374-93.
17. Clawson BJ. Experiments relative to vaccination with the Calmette-Guerin bacillus (BCG). Arch Path 1935; 20 : 343.
18. Greene MI, Schalten S, Bromberg JS. Delayed hypersensitivity. In: Paul WE. Fundamental immunology. New York : Raven Press, 1984 : 685-95.
19. Beck JS, Morley SM, Gibbs JH, *et al.* The cellular responses of tuberculosis and leprosy patients and of healthy controls in skin tests to new tuberculin and leprosin A. Clin Exp Immunol 1986; 64 : 484-94.
20. Fullmer MA, Shen JY, Modlin RL, Rea TH. Immunohistological evidence of lymphokine production and lymphocyte activation antigens in tuberculin reactions. Clin Exp Immunol 1987; 67 : 383-90.
21. Waksman B. Delayed (cellular) hypersensitivity. In: Sainten M, ed. Immunological diseases. Boston: Little Brown, 1971 : 220-52.
22. Epstein WL. Granulomatous hypersensitivity. Prog Allergy 1967; 11 : 36-88.
23. Stiehl P. Immunopathologic aspects of local tuberculous tissue reactions. Zentralbl Allg Pathol 1985; 130 : 313-21.
24. Permongkol C, Bovornkitti S, Matangkasombut P. Cell-mediated immune status in patients with bronchogenic carcinoma. Siriraj Hosp Gaz 1981; 33 : 851-7.
25. Bovornkitti S, Kangsadal P, Sathirapat P, Oonsombat P. Reversion and reconversion rate of tuberculin skin reactions in correlation with the use of prednisone. Dis Chest 1960; 38 : 51-5.
26. Vidhidharm A, Matangkasombut P, Bovornkitti S. T-cell subpopulations in tuberculosis and the effects of rifampicin. Asian Pac J Allergy Immunol 1985; 3 : 165-73.
27. Galal SH, Khalil SH, El-Husseiny W, Brock J. Cell mediated and humoral immunity and light-chain proteinuria in rifampicin-treated tuberculous patients. Allergy Immunol (Leipz) 1988; 34 : 249-54.
28. Kent DC, Schwartz R. Active pulmonary tuberculosis with negative tuberculin skin reaction. Am Rev Respir Dis 1967; 95 : 411-8.
29. Howard WL, Klopfenstein MD, Steiniger WJ, Woodrulf CE. The loss of tuberculin sensitivity in certain patients with active pulmonary tubeculosis. Chest 1970; 57 : 530-4.
30. Rooney JJ, Croceo JA, Kramer S. Further observations on tuberculin reactions in active tuberculosis. Am J Med 1976; 60 : 517-22.
31. Daniel TM, Oxtoby MJ, Pinto E, Moreno E. The immune spectrum in patients with pulmonary tuberculosis. Am Rev Respir Dis 1981; 123 : 556-9.
32. Onwubalili JK, Scott GM. Immune status in tuberculosis and response to treatment. Tubercle 1988; 69 : 81-94.
33. McMurray DN, Echeverri A. Cell-mediated immunity in anergic patients with pulmonary tuberculosis. Am Rev Respir Dis 1978; 118 : 827-34.
34. Nash DR, Douglas JE. Anergy in active tuberculosis: a comparison between positive and negative reactors and an evaluation of 5 TU and 250 TU test doses. Chest 1980; 77 : 32-7.
35. Bovornkitti S, Matangkasombut P. Anergy in active pulmonary tuberculosis. Chest 1981; 79 : 251-2.
36. Fujiwara H, Kleinhenz ME, Wallis RS, Ellner JJ. Increased interleukin-1 production and monocyte suppressor cell activity associated with human tuberculosis. Am Rev Respir Dis 1986; 133 : 73-7.
37. Vilcek J, Klion A, Henriksen-DeStefano D, *et al.* Defective gamma-interferon production in peripheral blood leukocytes of patients with acute tuberculosis. J Clin Immunol 1986; 6 : 146-51.
38. Toossi Z, Kleinhenz ME, Ellner JJ. Defective interleukin-2 production and responsiveness in human pulmonary tuberculosis. J Exp Med 1986; 163 : 1162-72.
39. Shiratsuchi H, Okuda Y, Tsuyuguchi I. Recombinant human interleukin-2 reverses *in vitro*-deficient cell-mediated immune responses to tuberculin-purified protein derivative by lymphocytes of tuberculous patients. Infect Immun 1987; 55 : 2126-31.
40. Zeitz S, Ostow JH, Van Arsdel PP Jr. Humoral and cellular immunity in the anergic tuberculous patients. J Allergy Clin Immunol 1974; 53 : 20-6.
41. Margolis ML, Van Uitert BL. Anergy in tuberculosis. Biomed Pharmacother 1985; 39 : 292-8.
42. Rossi GA, Balbi B, Manca F. Tuberculous pleural effusions. Evidence for selective presence of PPD-specific T-lymphocytes at site of inflammation in the early phase of the infection. Am Rev Respir Dis 1987; 136 : 575-9.
43. Nielsen H, Bennedsen J, Larsen SO, Rhodes JM, Viskum K. Defective monocyte chemotaxis in pulmonary tuberculosis. Eur J Respir Dis 1982; 63 : 122-9.
44. Rook GAW, Carswell JW, Standord JL. Preliminary evidence for the trapping of antigen specific lymphocytes in the lymphoid tissues of "anergic tuberculosis". Clin Exp Immunol 1976; 26 : 129-32.
45. El-Naggar A, Higashi GI. Tuberculosis meningitis E rosette forming lymphocytes in cerebrospinal fluid. Neurology (NY) 1981; 31 : 610-2.
46. Fujiwara H, Tsuyuguchi I. Frequency of tuberculin-reactive T-lymphocytes in pleural fluid and blood from patients with tuberculous pleurisy. Chest 1986; 89 : 530-2.
47. Smith JA, Reichman LB. Lymphocyte transformation. An aid in the diagnosis of tuberculosis in patients with non-reactive skin tests. Am Rev Respir Dis 1972; 106 : 194-201.
48. Beck JS, Potts RC, Kardjito T, Grange JM. T4 lymphopenia in patients with active pulmonary tuberculosis. Clin Exp Immunol 1985; 60 : 49-54.

49. Onwubalili JK, Edwards AJ, Palmer L. T4 lymphopenia in human tuberculosis. Tubercle 1987; 68 : 195-200.

50. Permmongkol C, Matangkasombut P, Bovornkitti S, Watanawongse W, Singhaseni D. Correlation between lymphocyte transformation and tuberculin skin test among tuberculous patients and healthy subjects. Siriraj Hosp Gaz 1975; 27 : 1108-18.

51. Ellner JJ. Pleural fluid and peripheral blood lymphocyte function in tuberculosis. Ann Intern Med 1978; 89 : 932-3.

52. Shimokata K, Kawachi H, Kishimoto H, Maeda F, Ito Y. Local cellular immunity in tuberculous pleurisy. Am Rev Respir Dis 1982; 126 : 822-4.

53. Shiratsuchi H, Tsuyuguchi I. Analysis of T cell subsets by monoclonal antibodies in patients with tuberculosis after *in vitro* stimulation with purified protein derivative of tuberculin. Clin Exp Immunol 1984; 57 : 271-8.

54. Shimokata K, Kishimoto H, Takagi E, Tsunekawa H. Determination of T-cell subset producing gamma-interferon in tuberculous pleural effusion. Microbiol Immunol 1986; 30 : 353-61.

55. Fujiwara H, Kleinhenz ME, Wallis RS, Ellner JJ. Increased interleukin-1 production and monocyte suppressor cell activity associated with human tuberculosis. (Letter to the editor- from the authors). Am Rev Respir Dis 1987; 135 : 1218-9.

56. Kleinhenz ME, Ellner JJ. Antigen responsiveness during tuberculosis: regulatory interactions of T cell subpopulations and adherent cells. J Lab Clin Med 1987; 110 : 31-40.

57. Schmitt E, Meuret G, Stix L. Monocyte recruitment in tuberculosis and sarcoidosis. Br J Haematol 1971; 35 : 11-7.

58. Tweardy DJ, Schacter BZ, Ellner JJ. Association of altered dynamics of monocyte surface expression of human leukocyte antigen DR with immunosuppression in tuberculosis. J Infect Dis 1984; 149 : 31-7.

59. Toossi Z, Edmonds KL, Tomford JW, Ellner JJ. Suppression of purified protein derivative-induced interleukin-2 production by interaction of CD16 (Leu 11 reactive) lymphocytes and adherent mononuclear cells in tuberculosis. J Infect Dis 1989; 159 : 352-6.

60. Kleinhenz ME, Ellner JJ, Spagnuolo PJ, Daniel TM. Suppression of lymphocytes responses by tuberculous plasma and mycobacterial arabinogalactan: monocyte dependence and indomethacin reversibility. J Clin Invest 1981; 68 : 153-62.

61. Goodwin JS, Webb DR. Regulation of the immune response by prostaglandins. Clin Immunol Immunopathol 1980; 15 : 106-22.

62. Gordon D, Bray MA, Morley J. Control of lymphokine secretion by prostaglandins. Nature 1976; 262 : 401-2.