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SHORT ANALYTICAL REVIEW

The Immunopathology of Systemic Anergy in Infectious Diseases: A Reappraisal and New Perspectives[1]

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INTRODUCTION

We owe to Clemens Von Pirquet the initial immunoclinical and immunopathological description of anergy (1). Anergy has been generally defined as: "The state of an organism that has lost the ability to specifically react with an antigen to which it was previously sensitized." At this point, we must emphasize that we are focusing on abnormalities of the secondary or "memory" phase of the immune response. Commonly, anergy is demonstrated by the inability to mount a delayed-type hypersensitivity (DTH) response to a battery of recall antigens (cutaneous anergy). For many years, the physiopathology of anergy remained unknown, but the probable mechanisms related to the onset and natural history of anergy were linked to a broad defect in cell-mediated immunity (CMI).

The CMI defect underlying the clinical expression of anergy has been stressed in numerous reports [reviewed in Ref. (2)]. Many of those reports are contradictory and conflicting. Potential pitfalls in assessing anergy in both chronic and infectious diseases include: the use of poorly standarized and/or unrelated antigen preparations, the use of fresh peripheral blood mononuclear cells (PBMC), and the inclusion of treated patient populations. In the last 10 years, it has been possible to accumulate an increasing body of evidence which casts serious doubts on the established lines of reasoning in relation to the etiopathogenesis of the "anergic phase" in human diseases (3–11).

It is the purpose of this review to discuss recent observations on the immunopathology of systemic anergy. In order to explain some basic issues related to anergy, we recently proposed to define anergy as: "The state of an organism where its T cells have lost their ability to specifically react to an antigen to which it was previously sensitized" (3).

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Our proposal emerged from research conducted in several laboratories, including our center (12–15), based primarily on infectious and tropical diseases. One of the critical questions addressed as whether antigen-specific unresponsiveness, rather than a generalized CMI depression, was the underlying mechanism to explain the lack of *in vivo* and *in vitro* responses from sensitized T cells in this group of patients.

We initially selected active or inactive patients with paracoccidioidomycosis (PCM) (12). Precultured cells from active, anergic PCM patients (also exhibiting high titers of serum anti-PCM antibodies and elevated levels of circulating immune complexes) not only showed a vigorous blastogenesis to phytohemaglutinin but an intact memory response to the PCM antigen. Remarkably, Mohagheghpour *et al.* have recently reported similar observations in patients with lepromatous leprosy (6). Leprosy is considered to be the paradigm of clinical anergy, with absent CMI responses to products of *Mycobacterium leprae*. However, these investigators found that although fresh T cells from most lepromatous leprosy were unresponsive to *M. leprae* antigen, after a 48-hr preculture period, the same cell preparation, in the absence of the bacilli, expressed a distinct and significant blast transformation response to the specific antigen. The effect of preculture was specific for the response to *M. leprae* and was limited to the CD4 cells of nonresponder lepromatous patients. It should be mentioned that the presence of *M. leprae* reactive T cells in lepromatous patients has been previously reported (16–18). Furthermore, recombinant IL-2 enriched T cell-conditioned media could also reverse the unresponsiveness of lepromatous leprosy (19). More recently, we found that tuberculosis patients (15) with a significant depression of T cell reactivity to PPD improved such a capacity after their PBMC were precultured, confirming the observations in PCM and leprosy.

Based on these findings, our working hypothesis on the probable immunopathology of systemic anergy has been related to immunomodulation of *in vivo* cell be-

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havior arising from humoral and cell-mediated events that follow antigen–host interaction.

Within this context, we will focus on some of the possible immunomodulatory factors and their relationship to systemic anergy.

AUTOLOGOUS SERUM FACTORS (ASF)

In the late 1960s, the Hellstroms clearly showed that ASF added to *in vitro* cultures could block cellular cytotoxicity in the Moloney sarcoma virus model (20). We conducted studies on ASF in selected clinical models by exposing precultured PBMC (responding to the different kinds of stimuli) from patients or controls to autologous heat-inactivated serum. ASF were almost universally present, inhibiting or, less frequently, enhancing blast transformation. This bimodal property of ASF could be predominantly inhibitory (12–15) as well as nonspecific since ASF commonly also inhibited PBMC responses from controls. ASF with the same characteristics have been found in malignant tumors [reviewed in Ref. (2, 8–9, 21)], systemic lupus erythematosus (SLE) (22–24), non-Hodgkins lymphomas (25), and leprosy (4, 5, 26, 27). This modulatory action of ASF has been explored in depth in SLE. Williams *et al.* reported in 1973 the inhibitory action of lupus sera on allogeneic MLC as well as on PHA and Con A stimulation (22). Horwitz *et al.* showed a relationship between impaired cellular immunity and ASF (28) and Okudaira *et al.* demonstrated that IgG and IgM present in the sera of active SLE patients blocked the binding of monoclonal anti-Ia to Ia positive target cells and that IgG also blocked the autologous MLC (24). We confirmed these findings, which were more pronounced with precultured cells and also reported that in some SLE patients, ASF may enhance *in vitro* proliferation to alloantigens (29, 30). More recently, Kerr *et al.* (4) and Hussein *et al.* (5), investigating lepromatous leprosy sera, showed the blocking capability of IgG on the recruitment of cells into the growth cycle, probably exerting its influence early in the cell cycle through a distinct membrane structure. Using cloned T cell lines, Janeway and co-workers showed that monoclonal antibodies reacting with epitopes of the T cell receptor can inhibit or enhance the activation of these cells, depending on the molecular characteristic of the interacting epitope (31). The nature of ASF remains unknown. However, one of the possibilities relates to circulating immune complexes (CIC). CIC are particularly prevalent in the anergic "polar" form of many chronic or infectious diseases. For instance, in patients with lepromatous leprosy, disseminated forms of tuberculosis, leishmaniasis, paracoccidioidomycosis, etc., high levels of CIC are frequently detected (12, 32, 33). Moreover, using the Raji cell assay (34) and a C1q-binding microassay (35), we found immune complex-like material in preculture supernatants of PBMC from patients with onchocerciasis (13).

AUTOLOGOUS CELL FACTORS (ACF)

Another potential immunomodulatory mechanism capable of significantly modifying T cell function relates to the cell subpopulations and their soluble products which actively participate in the host response to antigens. In lepromatous leprosy, cloned CD8 cells isolated from skin cell infiltrates could suppress blast transformation to concanavalin A and to *M. leprae* (36). Moreover, Ottenhoff *et al.* (37) showed that *M. leprae*-induced T suppressor clones were able to inhibit responses of both peripheral blood and cloned T helper cells, reacting to *M. leprae* and related mycobacterial antigens.

To further investigate the possible role of ACF on *in vitro* cell responses, we selected three different clinical models. First, Amerindian carriers of active untreated onchocerciasis (a filariasis caused by *Onchocerca volvulus*). Findings in this unique group of patients (13) showed that some of the precultured lymphocyte were hyporeactive to alloantigens. Coculture experiments were performed in which allogeneic responses of lymphocytes from healthy donors were tested in the presence of 10 different patient cells and were compared with the response in cocultures with cells from third party healthy donors. The Amerindians PBMC inhibited the response to alloantigens by cells from normal controls.

Second, patients with recent or chronic *Schistosoma mansoni* infection were studied (14), focusing on their proliferative response to adult worm antigen (SAWA). Precultured peripheral CD4 cells showed a significantly higher response to the specific antigen when compared to fresh cell preparations. Furthermore, the addition of each patient's serum to the *in vitro* response to both SAWA or recall antigens produced strong inhibition (also exerted on allogenic cells derived from healthy subjects). In addition, adherent monocyte–macrophage cells, rather than CD8 cells, inhibited CD4 proliferation to SAWA; the latter finding was initially postulated by Tood *et al.* employing nonpurified mononuclear cells (38).

Lastly, 10 patients with current active pulmonary tuberculosis were investigated and compared with 10 BCG-immunized healthy individuals. It has been established that patients with advanced tuberculosis commonly show antigen-specific anergy (39, 40). ASF, ACF, and redistribution of peripheral T cell pools have been proposed as major factors influencing cell behavior against *M. tuberculosis* challenge (41–43). Besides investigating the response of precultured cells to PPD and other recall antigens and the influence of ASF, we concentrated on the action of autologous isolated adherent monocytic cells and the *in vitro* synthesis of IL-2 and serum-soluble IL-2 receptor levels (IL-2R). The alterations found in relation to IL-2 synthesis and soluble IL-2R, associated to the specific PPD hyporeactivity, even at this early clinical status, suggested the

possibility of lymphocyte preactivation which may prevent blastogenic responses to antigen added *in vitro*. Further, high levels of soluble IL-2R in patient sera may reflect such a state of lymphocyte preactivation. Upon stimulation with PPD, *in vitro* IL-2 synthesis was significantly lower, as reported by Toosi *et al.* (44), in patients with advanced tuberculosis. Both soluble and membrane IL-2 receptors have the ability to bind circulating IL-2. Thus, an excess of soluble IL-2R may prevent IL-2 from binding to membrane receptors, interfering with *de novo* IL-2 synthesis and the response of an expanded antigenic-specific lymphocyte pool. In addition, diminished IL-2 production could also be related to the presence of activated macrophages with supressive action (45). Furthermore, depletion of adherent cells increased IL-2 synthesis in tuberculosis patients considered high responders to tuberculin (44, 45). The monocyte–macrophage inhibitory influence has been related to prostanglandin E_2 (46–48). Within this context, we found that the addition of naproxen (a prostaglandin E_2 inhibitor) to the cultures increased the cell responses to PHA and PPD in a similar fashion as compared to the depletion of adherent cells (15).

FREE ANTIGEN

Antigen, by itself, may exhibit significant immunomodulatory properties. Several examples illustrate this fact. In the leprosy model, Menhra *et al.* demonstrated that the terminal trisaccharide found in *M. leprae* glycolipid-I was an active inducer of CD8 suppressor cells, in patients with both lepromatous and borderline leprosy (49). In addition, Mohagheghpour *et al.* showed, in lepromatous patients, that preincubation with varying concentrations of the *M. leprae* antigen significantly reduced the precultured CD4+ lymphocyte-mediated blastogenic response to standarized amounts of the same antigen (6). In tuberculosis, Ellner *et al.* demonstrated that the mycobacterial D-arabinomannan extract suppressed blast transformation and migratory inhibitory factor production in appropriately sensitized donors (50). Parasite products with similar activity have been described by Capron *et al.* in culture supernatants of *S. mansoni* (51), and Arango *et al.* showed a positive correlation between circulating antigen and lack of DTH reactions in onchocerciasis (52). Cholera toxin (CT), which is a potent oral immunogen (53, 54), has been found to exhibit distinct immunomodulatory properties. Lycke *et al.* recently reported that CT provoked a strong inhibition of cell proliferation, early after mitogen stimulation, whereas later, after Con A stimulation, CT promoted the proliferation of T cells (55). In their recent report, Mohagheghpour *et al.* (56) found a potent T and B immunostimulatory *M. leprae* fraction, suggesting a concentration-dependent bimodal effect of *M. leprae* in T cell cultures.

NEW PERSPECTIVES

We have attempted to review and stress the need to reassess our current understanding of the immunopathology of systemic anergy in infectious diseases. In most instances, the "lack of reactivity" of T cells appears to be a secondary phenomenon to a very complex array of internal immunomodulatory influences, triggered by the antigen–host interaction, which may inhibit or less frequently enhance T cell responses. It is our belief that in infectious diseases, where the nature of the antigenic source is known, a primary T cell defect (generalized or specific) is improbable. Reduction of the antigenic load, periods of sustained clinical remission, or the proper handling of *in vitro* cell culture conditions may reveal an intact capability in the host to express a memory response to the sensitizing antigen. In Table 1, we have depicted a revised version of the previously proposed clinical classification of systemic anergy (3). Acquired immunodeficiency syndrome (AIDS) is also included, as the only clinical example thus far of CMI unresponsiveness, due at least in part to the active destruction of immunocompetent lymphoid cells.

The recent description of migration of antigen-specific T cells to the site of disease activity and the subsequent redistribution of effector cell pools is also broadening our comprehension on the dynamics of antigen-driven specific immune responses in the different body compartments and its implications in the immunopathology of systemic anergy.

In patients with active tuberculosis and a peripheral lack of response to PPD, a preferential sequestration of antigen-specific T lymphocytes to the pleural space has been reported, showing local T helper cells responding to PPD. After successful drug therapy, both PBMC and DTH responses to PPD became positive (43). The immunomodulatory influence arising from these redistributed cell compartments in terms of peripheral

TABLE 1
Clinical Classification of Systemic Anergy

1. Primary
   Chronic lymphocytic leukemias
2. Secondary
   - 2.1 Immunomodulation (antigen–host interaction)
     - a. Infectious diseases
     - b. Lymphoproliferative disorders
     - c. Cancer
     - d. Granulomatous diseases
   - 2.2 Immunosenescence (aging)
   - 2.3 Active lymphoid cell destruction
     - a. AIDS
   - 2.4 Induced
     - a. Malnutrition
     - b. Burns
     - c. Surgery
     - d. Uremia
     - e. Immunosuppressive drugs

blood cells responses may prove to be of distinct significance in the induction of systemic anergy.

Modlin *et al.* determined that 2% of the lymphocytes in tuberculoid leprosy skin lesions could proliferate in response to *M. leprae*, while only 0.02% of PBMC were responsive to the same antigen. The ratio of helper cells (CD4, CD29) to suppressor–inducer cells (CD4, CD45R) was 1.2:1 in peripheral blood but was 14:1 in the skin lesions (57), further stressing the need to monitor redistribution and homing of mononuclear cells as a significant mechanism underlying both inflammatory and anergic responses.

Based on the accumulated evidences discussed above, we propose a unifying approach to better understand the induction of systemic anergy in infectious diseases. This approach stresses the role of ASF and ACF, the redistribution of sensitized lymphocytes, and the influence of free antigen in the final outcome of T lymphocyte response. Furthermore, it seems plausible to assume that all of these immunomodulatory influences may not only coexist in the same host but may also act simultaneously. The result of the influence of inhibitors and/or enhancers on T cell responses should determine the immunoclinical characteristics of the disease. The implications of the complexity of these and other possible internal immunomodulators, which in the susceptible host determine the presence of clinical systemic anergy, are multiple; their systematic study and further characterization seems essential. This, in turn, may provide not only new diagnostic tools but a different concept on the natural history of the anergic phase in infectious diseases. The rationale underlying the current treatment of these anergic patients also requires reassessment. Therapeutic measures to remove the immunomodulators associated with remission could be lifesaving in the acutely ill anergic patient. Finally, the current efforts to apply immunotherapy or vaccines in the treatment of these anergic patients may prove to be a costly failure, unless the existence in these patients of an intact capability to be sensitized and to show memory responses is realized and proper measures are taken to deal with the perturbing influences of internal immunomodulators.

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REFERENCES

1. Von Pirquet, C., *Allergy. Arch. Intern. Med.* 7, 259–341, 1911.
2. Dwyer, J. H., Anergy: The mysterious loss of immunological Energy. *Prog. Allergy* 35, 15–92, 1984.
3. Bianco, N. E., The immunomodulatory influence of serum factors and its relationship with clinical anergy. *In* "Proceedings, XII International Congress of Allergology and Clinical Immunology," pp. 101–107, J. All. Clin. Immunol., 1986.
4. Kerr, M. A., Hussein, J. M., Potts, R. C., Swanson, J., and Sheriff, M. M., Characterization of a factor in leprosy serum that inhibits the growth of mitogen stimulated normal human lymphocytes. *Immunology* 61, 117–123, 1987.
5. Hussein, J. M., Kerr, M. A., Swanson, J., and Sheriff, M., The mechanism of action of the factor in leprosy serum that inhibits the growth of mitogen-stimulated normal human lymphocytes. *Immunology* 61, 124–129, 1987.
6. Mohagheghpour, N., Gelber, R. R., and Engleman, E. G., T cell defect in lepromateus leprosy is reversible in vitro in the absence of exogenous growth factors. *J. Immunol.* 138, 570–574, 1987.
7. Rook, G. A. W., Progress in the immunology of the mycobacterioses. *Clin. Exp. Immunol.* 69, 1–9, 1987.
8. Machado, I. V., Ruíz-Diez, C., Blanca, I., and Bianco, N. E., Characterization of cell-mediated immunity in long term survivors of gastric or colorectal cancer. *Am. J. Surg.* 147, 334–338, 1984.
9. Feo-Figarella, E., Morillo, F., Blanca, I., and Bianco, N. E., Failure of cell-mediated effector mechanism in lung cancer. *JNCI* 73, 1–6, 1984.
10. Thomas, P. D., and Hunninghake, G. W., Current concepts of the pathogenesis of sarcoidosis. *Am. Rev. Resp. Dis.* 135, 747–760, 1987.
11. Hudspith, B. N., Brostoff, J., McNicol, M. W., and Johnson, M. W., Anergy in sarcoidosis: The role of interleukin-1 and prostanglandins in the depressed in vitro lymphocyte response. *Clin. Exp. Immunol.* 57, 324–330, 1985.
12. Arango, M., Oropeza, F., Anderson, O., Contreras, C. E., Bianco, N. E., and Yarzábal, L., Circulating immune complexes and in vitro cell reactivity in paracoccidioidomycosis. *Mycopathologia* 79, 153–158, 1982.
13. Pérez-Rojas, G. E., Valderrama, M., Echeverría, C., Machado, I., Contreras, C. E., Yarzábal, L., and Bianco, N. E., Immunology of onchocerciasis. II. Modulatory effects of serum and cell factors on lymphocyte proliferative responses to mitogens and alloantigens. *Inmunologia* 5, 120–124, 1986.
14. Aldrey, O., Noya, B., Machado, I., Noya, O., Bianco, N. E., and Pérez, G. E., Immunopathology of human schistosomiasis mansoni. I. Immunomodulatory influences on T cell function. *Rev. Inst. Med. Trop. Sao Paulo* 30, 393–399, 1988.
15. Andrade-Arzabe, R., Machado, I. V., Fernández, B., Blanca, I., Ramírez, R., and Bianco, N. E., Cellular immunity in current active pulmonary tuberculosis, *Am. Rev. Res. Dis.*, 143, 496–500, 1991.
16. Bach, M. A., Hoffenbach, A., Lagrange, P., Wallach, D., and Cottenot, F., Mechanisms of T-cell unresponsiveness in leprosy. Ann. Immunol. (*Paris*) 134, 75–84, 1983.
17. Nath, I. M., Satish, J., Jaraman, M., Bhutani, L. K., and Sharma, A. K., Evidence for the presence of *Mycobacterium leprae* reactive T lymphocytes in patients with lepromatous leprosy. *Clin. Exp. Immunol.* 58, 522–530, 1984.
18. Shankar, P., Agis, F., Wallach, D., Flageul, B., Cottenot, F., Augier, J., and Bach, M. A., *M. leprae* and PPD-triggered T-cell lines in tuberculoid and lepromatous leprosy. *J. Immunol.* 136, 4255–4263, 1986.
19. Mustafa, A. S., Haregewoin, A., and Godal, T., Response to letter of Dr. Ottenhoff et al. "unresponsiveness to *M. leprae* in lepromatous leprosy in vitro: Reversible or not?" *Int. J. Lepr.* 52, 422–424, 1984.
20. Hellstrom, K. E., and Hellstrom, I., Lymphocyte-mediated cytotoxicity and blocking serum activity to tumor antigens. *Adv. Immunol.* 18, 209–268, 1974.

21. Blanca, I., Grases, P., Matos, M., Contreras, C. E., Ochoa, M. A., Wright, H., and Bianco, N. E., Immunology of human gastric cancer: A preliminary report. *Cancer* **49**, 1810–1816, 1982.
22. Williams, R. C., Lles, R. B., and Messner, R. P., Inhibition of mixed leukocyte culture responses by serum and globulin fractions from certain patients with connective tissue disorders. *Arthritis Rheum.* **16**, 597–602, 1973.
23. Okudaira, K., Searles, R. P., Goodwin, J. S., and Williams, R. C., Antibodies in the sera of patients with systemic lupus erythematosus that block the binding of monoclonal anti-Ia to Ia positive targets also inhibits the autologous mixed lymphocyte response. *J. Immunol.* **129**, 582–586, 1982.
24. Okudaira, K., Searles, R. P., Tanimoto, K., Horiuchi, Y., and Williams, R. C., T lymphocyte interaction with immunoglobulin G antibody in systemic lupus erythematosus. *J. Clin. Lab. Invest.* **69**, 1026–1033, 1982.
25. Hutchinson, R. E., Tige, D. C., and Davey, F. R., Serum from patients with non-Hodgkin's lymphoma (NHL) inhibit T-cell colony formation. *Am. J. Hematol.* **25**, 143–193, 1987.
26. Navalkar, R. G., Immunology of leprosy. *Crit. Rev. Microbiol.* 8, 25–52, 1980.
27. Bullock, W. E., and Fasal, P., Studies of immune mechanisms in leprosy. III. The role of cellular and humoral factors in impairment of the in vitro immune response. *J. Immunol.* **106**, 888–899, 1971.
28. Horwitz, D. A., and Cousar, J. B., A relationship between impaired cellular immunity, humoral suppression of lymphocyte function and severity of systemic lupus erythematosus. *Am. J. Med.* **58**, 820–826, 1975.
29. Pérez-Rojas, G., Penchaszadeh, G., Tapanes, F., Contreras, C. E., Abadi, I., Armas, P., Boissiere, M., and Bianco, N. E., Pathophysiology of the immune response in systemic lupus erythematosus: A new approach. *In* "Streptococcal Disease and Immune Response" (S. Reed and J. Zabriski, Eds.), pp. 507–521, Academic Press, New York, 1980.
30. Defreitas, M. E., Kondracki, E., Pérez-Rojas, G., and Bianco, N. E., Further aspects of T cell function in systemic lupus erythematosus. *Imm. Comm.*, **11**, 113–120, 1982.
31. Janeway, C. A., Carding, S., Jones, B., Murray, J., Portoles, P., Rasmussen, R., Rojo, J., Saizawa, K., West, J., and Bottomly, K., CD4+ T cell: Specificity and function. *Immunol. Rev.* **101**, 39–80, 1988.
32. Theofilopoulos, A. N., and Dixon, F. J., The biology and detection of immune complexes. *Adv. Immunol.* 28, 84–193, 1979.
33. Lambert, P. H., Dixon, F. J., Zubler, R. H., *et al.*, WHO collaborative study for the evaluation of eighteen methods for detecting immune complexes in the serum. *J. Clin. Lab. Immunol.* **1**, 1–10, 1978.
34. Theofilopoulos, A. N., Wilson, C. B., and Dixon, F. J., The Raji cell immunoassay for detecting immune complexes in human sera. *J. Clin. Invest.* **57**, 169–176, 1976.
35. Orozco, A., Contreras, C. E., Sánchez, P., Meijlison, D., and Bianco, N. E., Solid phase C1q microassay for the rapid detection of circulating immune complexes. *J. Immunol. Methods* **59**, 237–243, 1983.
36. Modlin, R. L., Kato, H., Mehra, V., Nelson, E. E., Xue-dong, F., Rea, T. H., Pattengale, P. K., and Bloom, B. B., Genetically restricted suppressor T-cell clones derived from lepromatous leprosy lesions. *Nature* **322**, 459–461, 1986.
37. Ottenhoff, T. H. M., Elferink, D. G., Klaster, P. R., and de Vries, R. R. P., Cloned suppressor T cells from a lepromatous leprosy patient suppress *Mycobacterium leprae* reactive helper T cells. *Nature* **322**, 462–464, 1986.
38. Tood, C. W., Goodgame, R. W., and Ey, D. G., Immune response during human *Schistosomiasis mansoni*: Supression of schistosome antigen-specific lymphocyte blastogenesis by adherent phagocytic cells. *J. Immunol.* **122**, 1440–1448, 1979.
39. Collins, F. M., The immunology of tuberculosis. *Am. Rev. Resp. Dis.* **125**, 42–49, 1982.
40. Daniel, T. M., Oxtoby, M. J., Pinto, M. E., and Moreno, S. E., The immune spectrum in patients with pulmonary tuberculosis. *Clin. Exp. Immunol.* **27**, 230–237, 1977.
41. Kleinhenz, M. E., Ellner, J. J., Spagnuolo, P. J., and Daniel, T. M., Suppression of lymphocyte responses by tuberculosis plasma and mycobacterial arabinogalactan. *J. Clin. Invest.* **68**, 153–162, 1981.
42. Ellner, J. J., Suppressor adherent cells in human tuberculosis. *J. Immunol.* **121**, 2573–2579, 1978.
43. Rossi, G. A., Balbi, B., and Manca, F., Tubercolous pleural effusions: Evidence for selective presence of PPD-specific T-lymphocytes at site of inflammation in the early phase of the infection. *Am. Rev. Resp. Dis.* **136**, 575–579, 1987.
44. Toosi, Z., Kleinhenz, M. E., and Ellner, J. J., Defective interleukin 2 production and responsiveness in human pulmonary tuberculosis. *J. Exp. Med.* **163**, 1162–1172, 1986.
45. Ellner, J. J., and Wallis, R. S., Immunological aspects of mycobacterial infections. *Rev. Infect. Dis.* **11** (Suppl. 2), 445–459, 1989.
46. Goodwin, J., Bankhurst, A. D., and Messner, R. P., Suppression of human T cell mitogenesis by prostaglandin: Existence of a prostaglandin producing suppressor cell. *J. Exp. Med.* **146**, 1719–1734, 1977.
47. Passwell, J., Levanon, M., Davidsohn, J., and Ramot, B., Monocyte PGE2 secretion in Hodgkin's disease and its relation to decreased cellular immunity. *Clin. Exp. Immunol.* **51**, 61–68, 1983.
48. Hochberg, M. C., NSAIDs: Mechanisms and pathways of action. *Hosp. Pract.* **24**, 185–198, 1989.
49. Mehra, X., Brennan, P. J., Rada, E., Convit, J., and Bloom, B., Lymphocyte suppression in leprosy induced by unique *M. leprae* glycolipid. *Nature* **308**, 194–196, 1984.
50. Ellner, J. J., and Daniel, T. M., Immunosuppression by mycobacterial arabinomannan. *Clin. Exp. Immunol.* **35**, 250–257, 1979.
51. Capron, A., Bazin, H., Dessaint, J. P., and Capron, M., Macrophage adherence mediated by specific IgE. *ICRS Med. Sci.* **3**, 52–60, 1979.
52. Arango, M., Lugo, E., Ouassi, A., de Moutis, I., Capron, A., and Yarzábal, L., Immunology of onchocerciasis. I. Association of antigenemia with depression of delayed cutaneous hypersensitivity. *Inmunología* **5**, 78–82, 1986.
53. Pierce, N. F., The role of antigen form and functions in the primary and secondary intestinal immune response to oral cholera toxin and toxoid in rat. *J. Exp. Med.* **148**, 195–204, 1978.
54. Lycke, N., and Holmgren, J., Strong adjuvant properties of cholera toxin on gut mucosal immune responses to orally presented antigens. *Immunology* **59**, 301–310, 1986.
55. Lycke, N., Bromader, A. K., Ekman, L., Karlsson, U., and Holmgren, J., Cellular basis of immunomodulation by cholera toxin in vitro with possible association to the adjuvant function in vivo. *J. Immunol.* **142**, 20–27, 1989.
56. Mohagheghpour, N., Munn, M. W., Gelber, R. H., and Engleman, E. G., Identification of an immunostimulating protein from mycobacterium leprae. *Infect. Immun.* **58**, 703–710, 1990.
57. Modlin, R. L., Melancon-Kaplan, J., Young, S. M. M., *et al.*, Learning from lesions: Patterns of tissue inflammation in leprosy. *Proc. Natl. Acad. Sci. USA* **85**, 1213–1217, 1988.

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