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Drug-Induced Lymphopenia
Focus on CD4+ and CD8+ Cells

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Abstract

Drug-induced lymphopenia is a common adverse event. Some drugs, in particular those used in the treatment of malignancies and autoimmune diseases, inevitably affect the percentages and proportions of lymphocytes in the peripheral blood. Some other drugs exert only minor effects and their clinical relevance cannot be established with certainty. Most cytotoxic and immunosuppressive drugs affect CD4+ T cells more profoundly. Since their regeneration seems to be slower than that of CD8+ T cells, the frequent occurrence of CD4+ lymphopenia may merely reflect this phenomenon. As in HIV infection, critically low numbers of CD4+ cells, irrespective of the cause, predisposes to opportunistic infections. There is no such critically low value for CD8+ cells, and their essential role in various pathological conditions should also be established.

The proportions and functions of peripheral blood lymphocytes are frequently analysed in a variety of clinical conditions. Their easy accessibility is the key element for this analysis. It is well known, however, that lymphocyte proportions or absolute values in the peripheral blood do not represent tissue distributions (e.g. their presence or absence in inflamed areas), nor they are related to

the values found in lymphoid tissues. In spite of these disadvantages, there are a number of disease states where the assessment of lymphocyte status is of importance (e.g. HIV infection and lymphomas). In many other conditions, their assessment has remained experimental, i.e. their practical value in terms of diagnosis or outcome has yet to be determined.

1. Normal Values of Lymphocytes and Their Subpopulations

The absolute numbers and percentages of lymphocytes and lymphocyte subsets may depend on several factors acting at the time of investigation. Apart from a great number of disease states, stress,[1] exercise,[2] smoking and diet may also influence the results.[3] It is widely accepted, however, that absolute numbers and proportions of lymphocytes are relatively stable in normal conditions.[4] It is of importance that absolute lymphocyte and subset values are more stable, and their assessment is more reliable, than that of proportions. The exception to this is CD4+/CD8+ ratio, which can be calculated by percentages. Drug-induced lymphopenia, if mild and confined to subset(s), can be identified only by determining absolute lymphocyte values.

Normal values for lymphocytes and their subsets should be assessed in all laboratories, since there is a great variability in the normal values obtained from different countries. Some data based on a relatively large cohort of healthy participants are shown in table I. Based on the values observed by Bofill et al.,[4] the total absolute number of lymphocytes is 1.90 ± 0.55 ($\times 10^9$/L) and the lower limit is 1.00 using the 95% range value (table II). The absolute number of CD3+ (T) cells is 1.45 ± 0.46 and the lower limit is 0.78. The mean values for CD4+ and CD8+ T cells are 0.83 ± 0.29 and 0.56 ± 0.23; their lower limits are 0.41 and 0.23, respectively. Using these lower limits for identifying patients with AIDS was found to be useful.[4]

2. Clinical Sequelae of Lymphopenia

Lymphopenia is a relatively common finding in everyday practice. Its causes and significance, however, are poorly understood. No large-scale study has been done for decades. Recently, Castelino et al.[7] reported on the occurrence and causes of lymphopenia observed in a large inpatient population. In most cases lymphopenia was reversible, and most frequently it was associated with acute illness, notably sepsis and trauma (including surgery). Malignancy with or without chemotherapy was also a common cause. Treatment-induced lymphopenia (definitely due to corticosteroids, cytotoxic drugs or radiotherapy) was found in at least 20% of cases. Apart from the rare idiopathic CD4+ T-lymphocytopenia, there were also patients displaying consistent lymphopenia over a number of years. Although we have no data on the long-term consequences of such prolonged lymphopenias, it seems to be of value to distinguish between short- and long-term lymphopenias.

2.1 CD4+ Cells

CD4+ T cells have regulatory functions in immunology as helper cells that can initiate and potentiate immune reactions. CD4+ T lymphopenia predisposes to opportunistic infections irrespective of the underlying disease. The deleterious consequences of HIV-induced lymphopenia are well known and beyond the scope of this review. Lymphopenia may also be present in certain auto-

Table I. Absolute values of total lymphocytes, CD3+ (T), CD4+ and CD8+ cells, and CD4+/CD8+ ratio, in healthy individuals. Values are means ± standard deviation

Reference	Cell number ($\times 10^9$/L)				CD4+/CD8+ ratio
	total lymphocytes	CD3+ cells	CD4+ cells	CD8+ cells	
Bofill et al.[4]	1.90 ± 0.55	1.45 ± 0.46	0.83 ± 0.29	0.56 ± 0.23	1.48
Giorgi et al.[5]	2.25 ± 0.57	1.64 ± 0.48	1.02 ± 0.33	0.61 ± 0.34	1.66
Vuillier et al.[6]	1.95 ± 0.85	1.45 ± 0.69	0.81 ± 0.38	0.52 ± 0.34	1.54

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Table II. Absolute mean values and lower limits of normal values of lymphocytes and subsets in healthy adults[4]

Cell type	Cell number ($\times 10^9$/L)	
	mean	lower limit[a]
Total lymphocytes	1.90	1.00
CD3+ cells	1.45	0.78
CD4+ cells	0.83	0.41
CD8+ cells	0.56	0.23

a Lower value of 95% range.

immune diseases. When profound, CD4+ lymphopenia may also predispose to opportunistic infections. Prekates et al.[8] reported on a patient with untreated rheumatoid arthritis who developed *Pneumocystis* infection due to severe CD4+ lymphopenia. In another patient with systemic lupus erythematosus, severe CD4+ lymphopenia resulted in *Cryptococcus* infection.[9] Four cases of *Pneumocystis carinii* pneumonia were observed in patients receiving corticosteroid therapy for dermatomyositis.[10] In all 4 patients lymphopenia was observed before the initiation of corticosteroid treatment and low CD4+ and CD8+ cell counts were evident at the time of *Pneumocystis carinii* pneumonia. It is well known that systemic autoimmune diseases, in particular rheumatoid arthritis and systemic lupus erythematosus, themselves carry an increased risk of infection.[11]

From 1992, a definition of 'idiopathic CD4+ T-lymphocytopenia' was formulated by the US Centers for Disease Control and Prevention (CDC).[12] These patients have markedly depressed CD4+ T cell counts, with or without opportunistic infections, in the absence of any evidence of HIV infection. The aetiology of this syndrome is not entirely clarified; an accelerated apoptosis (programmed cell death) of CD4+ T cells has been suggested.[13] Such patients usually develop the same opportunistic infections as HIV patients do, ranging from *Pneumocystis carinii* to atypical *Mycobacterium* infections.[14,15]

2.2 CD8+ Cells

Although the clinical consequences of CD4+ lymphopenia are well documented, much less is known about that of CD8+ cells. We know of a congenital CD4+ T cell deficiency, but there is no corresponding isolated CD8+ T cell deficiency. CD8+ deficiency is known only as a form of combined immunodeficiency.[16]

CD8+ T cells are cytotoxic lymphocytes participating in antiviral and antiparasitic immunity. Although the term 'cytotoxic T' cell is generally used, it should be stressed that cytotoxicity is not a unique feature of these cells. CD4+ T cells, natural killer cells and many other nonlymphoid cells can and usually do exert cytotoxic effects in a variety of pathological conditions. Similar to CD4+ T cells, CD8+ T cells also regulate immune functions, although they do not initiate or help immune responses.

The importance of CD8+ cells in viral infections is well established. In Epstein-Barr virus–induced mononucleosis, there is a marked proliferation of (cytotoxic) CD8+ cells.[17] At the peak of lymphocytosis, a 10-fold increase in the number of CD8+ cells was found.[17] In acute cytomegalovirus infection, the CD8+ lymphocytosis is less marked.[18] Similarly, in herpes simplex virus (HSV II) infection there was a transient mild increase in CD8+ cells, followed by a decrease.[19] It is also well established that after bone marrow graft, the number of CD8+ T cells increases more rapidly than that of CD4+ T cells, and there is a correlation between this increase and the incidence of graft-versus-host disease (GVHD).[20] In GVHD, tissues are infiltrated by CD8+ cells,[21] stressing the role of these cells in the development of the immune response in this disorder.

CD8+ cells usually participate in T cell–mediated immune reactions, and therefore they may play a crucial role in some autoimmune diseases. One of the best known examples is the diabetogenic potential of CD8+ cells in rats developing type 1 (insulin-dependent) diabetes mellitus after thymectomy and irradiation.[22] In this experiment, CD4+ cells exerted a protective role. CD8+ T cells from non-obese diabetic mice readily transferred diabetes in very young animals.[23] In the same strain, CD8+ γ-δ T cells induced by insulin were able to suppress adoptive transfer of diabetes.[24]

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In some other experiments, depending on the T helper 1 (T_H1) or T_H2 nature of the CD4+ cells, the transfer of CD4+ cells to SCID mice resulted in the development of an inflammatory bowel disease.[25]

Although there are conflicting data from animal experiments regarding the protective and destructive role of CD4+ and CD8+ cells, there is only limited information available on their exact role in human autoimmune diseases. In polymyositis, a lymphocyte-mediated inflammatory autoimmune disease, accumulated CD8+ T cells were observed in the inflamed tissues,[26] indicating their pathogenetic role. In patients with type 1 diabetes mellitus a CD8+ lymphopenia was found, with a concomitant higher CD4+/CD8+ ratio. A similarly higher ratio was observed in their first-degree relatives, in whom the expected incidence of type 1 diabetes mellitus is much higher than in control individuals.[27] Togun et al.[28] have shown that in human type 1 diabetes mellitus, autoantigen-specific activation of CD8+ cells is reduced compared with normal cells, which implicates their protective (suppressive) rather than pro-inflammatory role in the pathogenesis of type 1 diabetes mellitus. In systemic lupus erythematosus, where CD4+ lymphopenia is very common, there was a correlation between disease activity and frequency of CD8+ CD45RA+RO+ 'transient' isoforms.[29]

It seems to be easier to assess the role of CD8+ cells in pathological conditions than in normal immune functions. It is of interest that in most lymphopenias CD4+ cells are primarily affected. When they reach a critically low value, opportunistic infections may ensue. Similar critical values of CD8+ T cells that are essential for normal immune functions should be determined.

3. Effect of Drugs on Lymphocyte Subpopulations

Drug-induced lymphopenia is a well established phenomenon, in particular with the use of cytostatic drugs. However, other types of drugs can also provoke lymphopenia. The effect of these drugs upon lymphocyte subsets remains in most cases contradictory. In the following the relevant data will be summarised.

3.1 Cytotoxic Drugs

The majority of drugs used for the treatment of malignant tumours profoundly affect leucocyte functions and their circulating numbers. Although, in this respect, neutropenia is the most serious adverse effect, it is of interest that a marked lymphopenia usually precedes febrile neutropenia.[30] Most cytotoxic drugs affect all lymphocytes, but the percentage of CD4+ T cells usually decreases more profoundly, and therefore a relative increase in CD8+ cells is often seen.[31,32]

Carboplatin and dacarbazine followed by immunotherapy with interleukin-2 and recombinant interferon-α in patients with metastatic melanoma resulted in a decrease in CD3+ and CD4+ cells and an increase in CD8+ cells. This increase correlated with clinical response.[31]

Epirubicin treatment also influences both CD4+ and CD8+ cells. It is of interest, however, that in a cohort of breast cancer patients, responders to epirubicin therapy displayed a higher CD4+/CD8+ ratio (i.e. a smaller decrease in CD4+ cells, and a marked decrease in CD8+ cells) compared with nonresponders.[33]

Methotrexate at the dosages used in treatment of rheumatoid arthritis does not have marked effects on immune functions. In a 6-month trial, methotrexate tended to decrease CD3+, CD4+ and CD8+ cell counts.[34] Others have also found decreased CD4+ and CD8+ T cells in treated rheumatoid arthritis patients, and have proposed an association between drug-related lymphopenia and *Pneumocystis* pneumonia.[35] Some investigators, however, have failed to observe any change in CD3+, CD4+ or CD8+ cell numbers.[36]

Mitomycin (in combination with fluorouracil and interleukin-2) caused a marked decrease in CD8+ cells and an increase in CD4+ cells in patients with liver metastases treated with hepatic arterial infusion.[37]

Cyclophosphamide is well known for causing profound lymphopenia. This may also increase the

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risk of infections, in particular opportunistic infections, when it is administered in high dosages.[38] In a study using low dosage intravenous pulse therapy in severe connective tissue diseases, lymphopenia was observed in 20%, and infections in 7.7%, of patients.[39] Although it affects all lymphocyte subsets, cyclophosphamide administered intravenously to rheumatoid arthritis patients resulted in a decrease of CD4+ cells after 6 weeks of treatment.[36]

Pentostatin administration in hairy cell leukaemia resulted in a marked lymphopenia. Both B and T cells were affected; however, CD8+ cells decreased to a lesser extent.[40,41]

Azathioprine caused lymphopenia when used in high (2 mg/kg/day) dosages for an extended period.[42] No increase in the frequency of infections has been reported with this drug.

Purine nucleoside analogues such as cladribine, a novel class of immunosuppressive drugs, induce apoptosis of resting T cells. They caused prolonged lymphopenia predominating in T cells, especially CD4+ cells.[43,44] In another study, cancer patients treated with cladribine displayed a more profound decrease in CD8+ cells.[45]

Paclitaxel-induced severe lymphopenia has also been observed. CD4+ T cells were most profoundly affected.[46] The severe lymphopenia resulted in opportunistic infections: interstitial pneumonia and cytomegalovirus infection.

It is of interest that the regenerative pathways of CD4+ and CD8+ T cells after intensive chemotherapy are different. CD8+ T cells have a doubling time approximately 2-fold higher than that of CD4+ T cells; therefore, their number tends to return to normal much earlier.[47]

3.2 Corticosteroids

Corticosteroid treatment profoundly inhibits lymphocyte functions. Particularly at high dosages, corticosteroids cause thymic involution and a persistent decrease in T cell numbers.[48] Corticosteroids also affect lymphocyte recirculation,[49] but in humans corticosteroid treatment usually does not result in marked lymphopenia.[50] However, serial lymphocyte measurements in stable renal transplant patients receiving long-term methylprednisolone revealed a marked decrease in T cells, affecting both CD4+ and CD8+ cells.[51]

Corticosteroid treatment definitely increases the risk of opportunistic infections, the risk depending on the dosage and the duration of treatment.[52] However, a clear-cut correlation between immunosuppressive treatment of systemic autoimmune diseases and infection is difficult to draw, since the diseases themselves are associated with an increased risk of infection.[11]

3.3 Monoclonal Antibodies

Monoclonal antibodies have been used for the treatment of graft rejection and various autoimmune diseases. Both nonselective and selective antibodies have been used. CAMPATH-1H has been used for treatment of patients with therapy-refractory rheumatoid arthritis. The treatment induced a prolonged and profound lymphopenia, and because of its nonselectivity both CD4+ and CD8+ cells were equally affected. Despite this marked lymphopenia, no serious adverse effects, such as opportunistic infections, were reported.[53]

Depending on the dose administered, antibody-induced lymphopenia is not necessarily due to T cell death. Muromonab CD3 (OKT3), a pan–T cell monoclonal antibody, upregulates T cell activation markers, resulting in enhanced binding to adhesion molecules on the vascular endothelium and thus accelerated removal of T cells from the circulation.[54] Mouse monoclonal, and more recently chimaeric, antibodies directed against CD4+ cells have been used in patients with rheumatoid arthritis, as well as in other autoimmune diseases. Although in early studies some patients experienced definite improvement,[55,56] in placebo-controlled studies no therapeutic benefit was shown.[57] These antibodies caused a marked, and in some cases prolonged, CD4+ lymphopenia, but opportunistic infections have not been observed. Such lymphocyte-depleting antibodies have been replaced in recent years by nondepleting anti-CD4 antibodies. Monoclonal antibody treatment is currently used for

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short periods, and therefore data on the consequences of long-term treatment are not available.

Since CD8+ cells play an important role in GVHD,[20,21] anti-CD8 antibody treatment has been used to reduce the incidence of this serious consequence of bone marrow transplantation.[58] Although this treatment seemed to increase the graft success and lowered the incidence of GVHD, its effect cannot be assessed since cyclosporin and corticosteroids were also administered to the patients.

3.4 Thymus Hormones

Thymus hormones modulate T cell maturation and T cell functions. Their effects upon T lymphocytes are extremely complex. Thymomodulin, a calf thymus lysate, enhanced the CD4+/CD8+ ratio in the early stage of HIV infection by causing an absolute increase in CD4+ lymphocytes and a decrease in CD8+ cells.[59] Similar 'normalisation', i.e. enhancement, was seen in other chronic inflammatory diseases with low CD4+/CD8+ ratio.[60] Thymostimulin, a calf thymus extract used in a variety of primary and secondary immune deficiencies, selectively decreased CD8+ T cell numbers in patients with atopic eczema while CD3+ and CD4+ cells remained unchanged.[61] Thymopentin, a synthetic thymic pentapeptide, prevented postoperative CD3+ and CD4+ lymphopenia but failed to prevent the fall in CD8+ cells.[62]

3.5 Linomide

Linomide inhibited both superantigen- and glucocorticoid-induced lymphopenia by interfering with apoptosis, and therefore blocked the reduction of circulating CD4+ and CD8+ T cells.[63]

3.6 Interferons

Interferons, in particular interferon-α, and to a lesser extent interferon-β and interferon-γ, have been widely used in a variety of diseases, such as malignancies, viral infections and autoimmune diseases. Interferon-α treatment of patients with condyloma caused a significant decrease in CD3+, CD4+ and CD8+ cells, but the CD4+/CD8+ ratio remained unchanged.[64] Interferon-γ treatment caused a selective and transient decrease in the percentage of circulating CD8+ cells, probably due to an enhanced migration or adhesion of lymphocytes into tissues rather than direct toxicity.[65] Combined interferon-α-2a and interferon-γ treatment of patients with metastatic renal cell carcinoma caused a marked decrease in CD8+ cells. Interestingly, this decrease was associated with clinical response.[66]

3.7 Other Drugs

3.7.1 Cimetidine

Cimetidine, a histamine H_2 receptor antagonist, exerts a marked immunomodulatory effect in experimental animals. The effect in humans is less documented. Administration of cimetidine 800 mg/day to healthy participants resulted in a decrease in the absolute number of CD8+ cells (from 0.37 to 0.26 $\times$ 10^9/L at day 7 of treatment), and accordingly the CD4+/CD8+ ratio showed a significant increase (2.8 *vs* 3.6).[67]

3.7.2 Carbamazepine

Leucopenia is well known as an adverse effect of this anticonvulsant drug. In a patient with chronic lymphocytic leukaemia, carbamazepine was reported to exert a reproducible suppressive effect on lymphocyte count.[68]

3.7.3 Imidazoles

Imidazole compounds are used in a variety of pathological states, e.g. in fungal infections. In animal studies, 2-acetyl-4-tetrahydroxybutylimidazole, an immunosuppressive component of caramel food colouring (Caramel Colour III), reduced the number of both CD4+ and CD8+ cells in peripheral blood. This effect was mainly exerted by preventing the recruitment of CD4+ T cells.[69]

3.7.4 Opioids

Opioids, e.g. morphine, exert an immunosuppressive action. Acute morphine administration in rats decreased the number of circulating lymphocytes, equally affecting all major T subpopulations.[70]

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Table III. Effect of various drugs on circulating lymphocytes

Drug	Effect on lymphocytes	Clinical consequence (infections)	Reference
Cytotoxic drugs			
Carboplatin/dacarbazine	CD3 ↓, CD4 ↓, CD8 ↑	Not known	31
Epirubicin	CD4 ↓, CD8 ↓	Not known	33
Methotrexate	CD3 ↓, CD4 ↓, CD8 ↓	Increased risk of infection	34,35
	None	None	36
Mitomycin/fluorouracil	CD4 ↑, CD8 ↓	Not known	37
Cyclophosphamide	CD3 ↓	Increased risk of infection	38
	CD4 ↓	Not known	36
Pentostatin	CD3 ↓, CD4 ↓	Not known	40,41
Azathioprine	Not specified	None	42
Purine nucleoside analogues	CD4 ↓, CD8 ↓	Not known	43,44
	CD8 ↓	Not known	45
Paclitaxel	CD4 ↓	Increased risk of infection	46
Corticosteroids	CD4 ↓, CD8 ↓	Not known	51
	Not specified	Increased risk of infection	52
Monoclonal antibodies			
CAMPATH-1H	CD4 ↓, CD8 ↓	Increased risk of infection	53
Depleting anti-CD4	CD4 ↓	None	56,57
Anti-CD8	CD8 ↓	Not known	58
Thymic hormones			
Thymomodulin	CD4 ↑, CD8 ↓	None	59
Thymostimulin	CD8 ↓	None	61
Other immunomodulatory drugs			
Interferons	CD3 ↓, CD4 ↓, CD8 ↓	Not known	64
Interferon-γ	CD8 ↓	Not known	65,66
Other drugs			
Cimetidine	CD8 ↓	Not known	67
Opioids	CD3 ↓, CD4 ↓, CD8 ↓	Not known	70
Carbamazepine	Not specified	Not known	68
Bisphosphonates	Not specified	Not known	71,72
Calcitonin	CD8 ↓	Not known	73
Ipriflavone	Not specified	None	75,76
	CD8 ↓	None	77

Not specified = lymphopenia without further distinction of affected subset(s); ↑ indicates increase; ↓ indicates decrease.

3.7.5 Drugs Used in Osteoporosis

Biphosphonates are widely used for the treatment of osteoporosis, and leucopenia and/or lymphopenia have been repeatedly reported with these drugs. Leucopenia and/or lymphopenia were observed when alendronate was administered short term at high dosages to patients with postmenopausal osteoporosis.[71] Similar effects were reported also with pamidronate.[72]

Salmon calcitonin, widely used in osteoporosis, was found to increase the CD4+/CD8+ ratio from 1.6 to 2.3 after 90 days. This change was explained by an insignificant decrease in CD8+ T cell count.[73]

Ipriflavone, a synthetic isoflavone derivative, has been used in several countries for prevention and treatment of osteoporosis. Its efficacy and long term tolerability has been documented.[74] Recently, a decrease in lymphocyte number was observed in patients treated with ipriflavone.[75,76] In another clinical study, a relatively frequent occurrence of lymphopenia (about 20% decrease in ab-

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solute lymphocyte count) was reported after several months of administration. CD8+ cells were more profoundly affected than CD4+ cells. After cessation of treatment, lymphocyte counts slowly normalised. In spite of this immunological adverse effect, no significant consequences (i.e. infections) were observed.[77]

4. Conclusions

Lymphopenia is a common finding, but its consequences are poorly understood. A number of drugs affect lymphocyte count, most of them by preferentially reducing the circulating number of CD4+ T cells (summarised in table III). Some drugs, in particular corticosteroids and cytotoxic drugs, cause lymphopenia and may also increase the risk of (opportunistic) infections. Large-scale studies are needed to elucidate the connections between drugs causing lymphopenia restricted to one or more T cell subsets and the consequences of such lymphopenia, including infections or malignancies. When interpreting the data of such studies the following cautions have to be borne in mind:

(i) drugs causing lymphopenia, in particular corticosteroids and cytotoxic drugs, also affect phagocytic functions and/or other nonspecific immune functions;

(ii) any change in the number or percentages of circulating lymphocytes and their subsets does not necessarily represent the changes within the whole immune system, or within an inflamed tissue;

(iii) some diseases themselves cause alterations in immune reactivity, resulting in an increased risk of infection irrespective of the treatment.

References

1. Landmann RM, Muller FB, Perini C, et al. Changes of immunoregulatory cells induced by psychological and physical stress: relationship to plasma catecholamines. Clin Exp Immunol 1984; 58: 127-35
2. Shinkai S, Watanabe S, Asai H, et al. Cortisol response to exercise and post-exercise suppression of blood lymphocyte subset counts. Int J Sports Med 1996; 17: 597-603
3. Laurence J. T-cell subsets in health, infectious disease, and idiopathic CD4+ T lymphocytopenia. Ann Int Med 1993; 119: 55-62
4. Bofill M, Janossy G, Lee CA, et al. Laboratory control values for CD4 and CD8 T lymphocytes: implications for HIV-1 diagnosis. Clin Exp Immunol 1992; 88: 243-52
5. Giorgi JV, Cheng HL, Margolick JB, et al. Quality control in the flow cytometric measurement of T-lymphocyte subsets: the Multicenter AIDS Cohort study experience. Clin Immunol Immunopathol 1990; 55: 173-86
6. Vuillier F, Lapresle C, Dighiero G. Comparative analysis of CD4-4B4 and CD4-2H4 lymphocyte subpopulations in HIV negative homosexual, HIV seropositive and healthy subjects. Clin Exp Immunol 1988; 71: 8-12
7. Castelino DJ, McNair P, Kay TWH. Lymphocytopenia in a hospital population – what does it mean? Aust NZ J Med 1997; 27: 170-4
8. Prekates A, Kyprianou T, Paniara O, et al. *Pneumocystis carinii* pneumonia in a HIV-seronegative patient with untreated rheumatoid arthritis and CD4+ T-lymphocytopenia. Eur Respir J 1997; 10: 1184-6
9. Guma M, Krakauer R. CD4+ lymphocytopenia in systemic lupus erythematosus. Ann Int Med 1994; 120: 168
10. Bachelez H, Schremmer B, Cadronel J, et al. Fulminant *Pneumocystis carinii* pneumonia in 4 patients with dermatomyositis. Arch Intern Med 1997; 157: 1501-3
11. Duffy KN, Duffy CM, Gladman DD. Infection and disease activity in systemic lupus erythematosus: a review of hospitalized patients. J Rheumatol 1991; 18: 1180-4
12. Fauci AS. CD4 + T-lymphocytopenia without HIV infection: no lights, no camera, just facts. N Engl J Med 1993; 328(6): 429-31
13. Laurence J, Mitra D, Steiner M, et al. Apoptotic depletion of CD4+ T cells in idiopathic CD4+ T lymphocytopenia. J Clin Invest 1996; 97: 672-80
14. Smith DK, Neal JJ, Holmberg SD. Unexplained opportunistic infections and CD4 T-lymphopenia without HIV infection: an investigation of cases in the United States. N Engl J Med 1993; 328: 373-9
15. Anzalone G, Cei M, Vizzacaro A, et al. M. Kansasii pulmonary disease in idiopathic CD4+ T-lymphocytopenia. Eur Respir J 1996; 9: 1754-6
16. Rosen FS, Wedgwood RJP, Eibl M, et al. Primary immunodeficiency diseases. Clin Exp Immunol 1995; 99 Suppl. 1: 2-24
17. Reinherz EL, O'Brien C, Rosenthal P, et al. The cellular basis for viral-induced immunodeficiency: analysis by monoclonal antibodies. J Immunol 1980; 125: 1269-73
18. Carney WP, Rubin RH, Hoffman RA, et al. Analysis of T lymphocyte subsets in cytomegalovirus mononucleosis. J Immunol 1981; 126: 2114-6
19. Sheridan JF, Beck M, Aurelian L, et al. Immunity to herpes simplex virus type 2 IV: impaired lymphokine production during recrudescence correlates with imbalance in T lymphocyte subsets. J Immunol 198; 129: 326-31
20. Soiffer RJ, Gonin R, Murray C, et al. Prediction of graft-versus-host disease by phenotypic analysis of early immune reconstitution after CD6-depleted allogeneic bone marrow transplantation. Blood 1993; 82: 2216-23
21. Hiroki A, Nakamura S, Shinohara M, et al. Significance of oral examination in chronic graft versus host disease. J Oral Pathol Med 1994; 23: 209-15
22. Fowell D, Powrie F, Saoudi A, et al. The role of subsets of CD4+ T cells in autoimmunity. Ciba Found Symp 1995; 195: 173-82
23. Yoneda R, Yokono K, Nagata M, et al. CD8 cytotoxic T-cell clone rapidly transfers autoimmune diabetes in very young NOD and MHC class I-compatible scid mice. Diabetologia 1997; 40: 1044-52
24. Harrison LC, Dempsey-Collier M, Kramer DR, et al. Aerosol insulin induces regulatory CD8 gamma delta T cells that pre-

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vent murine insulin-dependent diabetes. J Exp Med 1996; 184: 2167-74
25. Powrie F, Correa-Oliveira R, Mauze S, et al. Regulatory interactions between CD45RB high and CD45RB low CD4+ T cells are important for the balance between protective and pathogenic cell-mediated immunity. J Exp Med 1994; 179: 589-600
26. Iannone F, Cauli A, Yanni G, et al. T-lymphocyte immunophenotyping in polymyositis and dermatomyositis. Br J Rheumatol 1996; 35: 839-45
27. Kaaba SA, Al-Harbi SA. Abnormal lymphocyte subsets in Kuwaiti patients with type-1 insulin-dependent diabetes mellitus and their first-degree relatives. Immunol Lett 1995; 47: 209-13
28. Togun RA, Resetkova E, Kawai K, et al. Activation of CD8(+) T lymphocytes in insulin-dependent diabetes mellitus. Clin Immunol Immunopathol 1997; 82: 243-9
29. Neidhart M, Pataki F, Michel BA, et al. CD45 isoforms expression on CD4+ and CD8+ peripheral blood T-lymphocytes is related to auto-immune processes and hematological manifestations in systemic lupus erythematosus. Schweiz Med Wochenschr 1996; 126: 1922-5
30. Blay JY, Chauvin F, Le Cesne A, et al. Early lymphopenia after cytotoxic chemotherapy as a risk factor for febrile neutropenia. J Clin Oncol 1996; 14: 636-43
31. Eisenthal A, Skornick Y, Ron I, et al. Phenotypic and functional profile of peripheral blood mononuclear cells isolated from melanoma patients undergoing combined immunotherapy and chemotherapy. Cancer Immunol Immunother 1993; 37: 367-72
32. Mackall CL, Fleisher TA, Brown MR, et al. Lymphocyte depletion during treatment with intensive chemotherapy for cancer. Blood 1994; 84: 2221-8
33. Lissoni P, Tancini G, Archili C, et al. Changes in T lymphocyte subsets after single dose epirubicin. Eur J Cancer 1990; 26: 767-8
34. Yocum DR, Olson CS, Nordensson K. Effects of methotrexate + cyclosporine on mononuclear cell proliferation and lymphocyte surface markers in rheumatoid arthritis patients. Arthritis Rheum 1994; 37 Suppl.: S254
35. Houtman PM, Stenger AA, Bruyn CA, et al. Methotrexate may affect certain T lymphocyte subsets in rheumatoid arthritis resulting in susceptibility to *Pneumocystis carinii* infection. J Rheumatol 1994; 21: 1168-89
36. Lacki JK, Schochat T, Sobieska M, et al. Immunological studies in patients with rheumatoid arthritis treated with methotrexate or cyclophosphamide. Z Rheumatol 1994; 53: 76-82
37. Okuno K, Ohnishi H, Nakajima I, et al. Intrahepatic infusion of interleukin-2 (IL-2) with mitomycin C (MMC)/5-fluorouracil (5-FU) through an implantable pump for the treatment of liver metastases [abstract]. Proc Am Assoc Cancer Res 1992; 33: 246
38. Kulke MH, Vance EA. *Pneumocystis carinii* pneumonia in patients receiving chemotherapy for breast cancer. Clin Infect Dis 1997; 25: 215-8
39. Martin-Suarez I, D'Cruz D, Mansoor M, et al. Immunosuppressive treatment in severe connective tissue diseases: effects of low dose intravenous cyclophosphamide. Ann Rheum Dis 1997; 56: 481-7
40. Kraut EH, Neff JC, Bouroncle BA, et al. Immunosuppressive effects of pentostatin. J Clin Oncol 1990; 8: 848-55
41. Thaler J, Grunewald K, Gattringer C, et al. Long-term follow-up of patients with hairy cell leukaemia treated with pentostatin: lymphocyte subpopulations and residual bone marrow infiltration. Br J Haematol 1995; 84: 75-82
42. Johnson PJ, McFarlane IG, Williams R. Azathioprine for long-term maintenance of remission in autoimmune hepatitis. N Engl J Med 1995; 333: 958-63
43. Beutler E, Koziol JA, McMillan R, et al. Marrow suppression produced by repeated doses of cladribine. Acta Haematol 1994; 91: 10-5
44. Dighiero G. Adverse and beneficial immunological effects of purine nucleoside analogues. Hematol Cell Ther 1996; 38 (Suppl. 2): S75-81
45. von Rohr A, Ghosh AK, Thatcher N, et al. Serial immunophenotype analysis of peripheral blood T cells, T cell subpopulations, B cells, and natural killer (NK) cells in patients treated with 2-chlorodeoxyadenosine (2-CDA) [abstract]. Blood 1993; 82 Suppl. 1: 521a
46. Reckzeh B, Merte H, Pfluger KH, et al. Severe lymphocytopenia and interstitial pneumonia in patients treated with paclitaxel and simultaneous radiotherapy for non-small-cell lung cancer. J Clin Oncol 1996; 14: 1071-6
47. Mackall CL, Fleisher TA, Brown MR, et al. Distinctions between CD8+ and CD4+ T-cell regenerative pathways result in prolonged T-cell subset imbalance after intensive chemotherapy. Blood 1997; 89: 3700-7
48. Flaherty DK, McGarity KL, Winzenburger P, et al. The effect of continuous corticosterone administration on lymphocyte subpopulations in the peripheral blood of the Fischer 344 rat as determined by two color flow cytometric analyses. Immunopharmacol Immunotoxicol 1993; 15: 583-604
49. Sackstein R, Borenstein M. The effects of corticosteroids on lymphocyte recirculation in humans: analysis of the mechanism of impaired lymphocyte migration to lymph node following methylprednisolone administration. J Invest Med 1995; 43: 68-77
50. Bast Jr RC, Reinherz EL, Maver C, et al. Contrasting effects of cyclophosphamide and prednisolone on the phenotype of human peripheral blood leukocytes. Clin Immunol Immunopathol 1983; 28: 101-14
51. Tornatore KM, Reed K, Venuto R. 24-hour immunologic assessment of CD4+ and CD8+ lymphocytes in renal transplant recipients receiving chronic methylprednisolone. Clin Nephrol 1995; 44: 290-8
52. Godeau B, Coutant-Perronne V, Le Thi Huong D, et al. *Pneumocystis carinii* pneumonia in the course of connective tissue disease: report of 34 cases. J Rheumatol 1994; 21: 246-51
53. Isaacs JD, Manna VK, Rapson N, et al. CAMPATH-1H in rheumatoid arthritis – an intravenous dose-ranging study. Br J Rheumatol 1996; 35: 231-40
54. Buysmann S, Bemelman FJ, Schellekens PT, et al. Activation and increased expression of adhesion molecules on peripheral blood lymphocytes is a mechanism for the immediate lymphocytopenia after administration of OKT3. Blood 1996; 87: 404-11
55. Herzog C, Walker C, Muller W, et al. Anti-CD4 antibody treatment of patients with rheumatoid arthritis: I: effect on clinical course and circulating T cells. J Autoimmun 1989; 2: 627-42
56. Wendling D, Wijdenes J, Racadot E. Utilisation therapeutique d'un anticorps monoclonal anti-CD4 dans la polyarthrite rheumatoide refractaire: resultats preliminaires. Rev Rheum 1991; 58: 13-7
57. Moreland LW, Pratt PW, Mayes MD, et al. Double-blind, placebo-controlled multicenter trial using chimeric monoclonal anti-CD4 antibody, cM-T412 in rheumatoid arthritis patients receiving methotrexate. Arthritis Rheum 1995; 38: 1581-8

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58. Kalayciouglu ME, Fishleder A, Bolwell BJ. Unrelated selective CD8+ T cell depleted allogeneic bone marrow transplantation after busulfan and cyclophosphamide. J Cell Biochem 1994; (Suppl. 18B): 84
59. Valesini G, Barnaba V, Benvenuto R, et al. A calf thymus acid lysate improves clinical symptoms and T-cell defects in the early stages of HIV infection: second report. Eur J Cancer Clin Oncol 1987; 23: 1915-9
60. Cazzola P, Mazzanti, Bossi G. In vivo modulating effect of a calf thymus acid lysate on human T lymphocyte subsets and CD4+/CD8+ ratio in the course of different diseases. Curr Ther Res 1987; 42: 1011-7
61. Harper JI, Mason UA, White TR, et al. A double-blind placebo-controlled study of thymostimulin (TP-1) for the treatment of atopic eczema. Br J Dermatol 1991; 125: 368-72
62. Braga M, Costantini E, Di Francesco A, et al. Impact of thymopentin on the incidence and severity of postoperative infection: a randomized controlled trial. Br J Surg 1994; 81: 205-8
63. Gonzalo JA, Gonzalez-Garcia A, Kalland T, et al. Linomide inhibits programmed cell death of peripheral T cells in vivo. Eur J Immunol 1994; 24: 48-52
64. Bauer R, Boehm I, Niedecken HW, et al. The quantitative immune status during interferon therapy [abstract]. J Invest Dermatol 1989; 93: 540
65. Aulitzky WE, Aulitzky W, Gastl G, et al. Acute effects of single doses of recombinant interferon gamma on blood cell counts and lymphocyte subsets in patients with advanced renal cell cancer. J Interferon Res 1989; 9: 425-33
66. Ernstoff MS, Gooding W, Nair S, et al. Immunological effects of treatment of sequential administration of recombinant interferon gamma and alpha in patients with metastatic renal cell carcinoma during a phase I trial. Cancer Res 1992; 52: 851-6
67. Brockmeyer NH, Kreuzfelder E, Guttman W, et al. Cimetidine and the immuno-response in healthy volunteers. J Invest Dermatol 1989; 93: 757-61
68. Silverman DA, Chapron DJ. Lymphopenic effect of carbamazepine in a patient with chronic lymphocytic leukaemia. Ann Pharmacother 1995; 29: 865-7
69. Gugasyan R, Losinno C, Mandel T. The effect of 2-acetyl-4-tetrahydroxybutylimidazole on lymphocyte subsets during a contact hypersensitivity response in the NOD mouse. Immunol Lett 1995; 46: 221-7
70. Flores LR, Wahl SM, Bayer BM. Mechanisms of morphine-induced immunosuppression: effect of acute morphine administration on lymphocyte trafficking. J Pharmacol Exp Ther 1995; 272: 1246-51
71. Vasikaran SD, Khan S, McCloskey EV, et al. Sustained response to intravenous alendronate in postmenopausal osteoporosis. Bone 1995; 17: 517-20
72. Liote F, Boval-Boizard B, Fritz P, et al. Lymphocyte subsets in pamidronate-induced lymphopenia. Br J Rheumatol 1995; 34: 993-5
73. Cutolo M, Barisone G, Seriolo B, et al. Juxta-articular osteoporosis in rheumatoid arthritis: reversal by local subcutaneous calcitonin. Curr Ther Res 1990; 48: 1126-35
74. Agnusdei D, Bufalino L. Efficacy of ipriflavone in established osteoporosis and long-term safety. Calcif Tissue Int 1997; 61: S23-7
75. Gennari C, Adami S, Agnusdei D, et al. Effect of chronic treatment with ipriflavone in postmenopausal women with low bone mass. Calcif Tissue Int 1997; 61: S-19-22
76. Adami S, Bufalino L, Cervetti R, et al. Ipriflavone prevents radial bone loss in postmenopausal women with low bone mass over 2 years. Osteoporosis Int 1997; 7: 119-25
77. Kovàcs B. A placebo-controlled dose-finding study of ipriflavone in the presentation of further bone content loss following the menopause [oral presentation]. Congress of the Hungarian Society for Osteoporosis; 1996 Sep 20-26; Tata

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