

LECTURE: 15

Title SECONDARY IMMUNODEFICIENCY DISORDERS

LEARNING OBJECTIVES:

The student should be able to:

- Describe the term "immunodeficiency".
- Classify the immunodeficiency disorders such as:
 - Primary immunodeficiency.
 - Secondary immunodeficiency.
- Define the primary and secondary immunodeficiencies.
- Identify the causes of the defective antibody responses.
- Explain if the defective antibody responses are due to failure of B cell function or due to defect in proper T cells signals to B lymphocytes supporting the explanation with examples of each.
- Identify the clinical manifestation which is considered one of clinical markers that indicates a defect in antibody responses.
- Identify the causes of the defective Cell-mediated immunity.
- List some pathogenic examples of cellular immunodeficiency disorders.
- Identify the clinical manifestation which is considered one of clinical markers that indicates a defect in cell-mediated responses.
- Should know the secondary immunodeficiency.
- Should know immunodeficiency due to HIV virus.
- Should know hereditary complement component defects which cause immunodeficiency.
- Should know the hereditary complement deficiencies which cause the immunodeficiency.
- Should have an idea about the effect of the oxygen reduction pathway of phagocytosis.
- Discuss immunodeficiency due to deficient leucocyte adhesion molecules.
- List some serological laboratory test help in the diagnosis of the different types of immunodeficiencies.

LECTURE REFERENCE:

1. TEXTBOOK: ROITT, BROSTOFF, MALE
IMMUNOLOGY. 6th edition. Chapter 20. pp. 313-321.
2. HANDOUT.

Secondary immunodeficiency

- **Immunomodulatory drugs** can severely depress immune functions.
- **Steroids** affect cell traffic, induce leucocytopenia and inhibit cytokine synthesis.
- **Cyclophosphamide, azathioprine and mycophenolate mofetil** act directly on DNA or its synthesis.
- **Severe protein – energy malnutrition (PEM)** reduces the efficacy of the immune system. Malnutrition increases the risk of infant mortality from infection through reduction in cell-mediated immunity, reduced CD4 helper cells, reduced T-cell help and a reduction of secretory IgA.
- **Trace elements, iron, selenium, copper and zinc** are important in immunity. Lack of these elements can lead to diminished neutrophil killing of bacteria and fungi, susceptibility to viral infections and diminished antibody responses.
- **Vitamins A, B6, C, E** and also folic acid are important in overall resistance to infection. Carotenoids are antioxidants like vitamin C and E and can enhance NK cell activity, stimulate the production of cytokines and increase the activity of phagocytic cells.
- **Diet and nutrition** are powerful innovative tools to reduce illness and death caused by infection.
- **AIDS** is caused by human immunodeficiency virus (HIV), which is a double-stranded RNA retrovirus that binds to CD4 and depletes CD⁺ T cells.
- **Severe CD4 depletion** results from a variety of mechanisms, with drastic functional impairment of cell-mediated immunity and death from opportunistic infections.
- **Combination therapy** for AIDS with reverse transcriptase and protease inhibitors is reasonably successful, but costly.
- **Successful vaccines** for HIV have not yet been identified.

IMMUNODEFICIENCY CAUSED BY DRUGS

There have been substantial advances over the past decade in understanding how the immune systems are regulated and how drugs may selectively alter function, producing not only immunodeficiency but also, in some circumstances, immune enhancement. This chapter examines the most important agents commonly used for systemic immunotherapy.

Corticosteroids are powerful immune modulators

The immune system is regulated by at least four fundamental mechanisms: hormonal (e.g. glucocorticoids), the cytokine system (including interleukins and interferons), network connectivity (through idiotypic-anti-idiotypic responses) and antigens. Glucocorticoids are the most powerful naturally occurring modulators of the immune response and have profound effects at most levels and on most components. In addition to their direct hormonal action on immune cell traffic and function, steroids have a substantial influence on cytokine synthesis, thereby also exerting a powerful indirect effect.

Significant changes in cell traffic are produced

Administration of steroids causes striking changes in circulating leucocyte populations, even when quite small quantities are used – for example, to produce physiological concentrations in previously adrenalectomized patients. These effects vary between cell types (Figure-1).

Steroid treatment causes circulating *lymphocytopenia*, maximal at 4-6 hours and returning to normal by 24 hours. T cell is affected more than B cells and, within the T-cell subsets, CD4 cells are more depleted than CD8 cells. Experimental studies suggest these cells are redistributed to marrow and spleen.

Monocytopenia occurs after steroid treatment, is most evident at 2 hours and recovers by 24 hours but, unlike effects on lymphocyte traffic, further repeated daily dosage does not cause subsequent cycles of depletion.

Neutrophilia is a feature of steroid treatment, due partly to release of mature stored cell from bone marrow and partly to reduction in cells leaving the circulation. However, rapid and prolonged decrease in circulating eosinophils and basophils after steroid treatment occurs in normal individuals, which contrasts markedly with the neutrophilia seen at the same time.

T-cell activation and B-cell maturation are inhibited

T-cell activation and proliferation are inhibited by steroids, which make them unresponsive to IL-1 and therefore unable to synthesize IL-2. Steroids inhibit the earliest stages of B-cell maturation, by blocking monocyte and T-cell involvement, but have little effect on mature B cells. However, after prolonged high dosage there is modest decrease in each immunoglobulin isotype.

Steroids inhibit production of IL-1 and TNF by monocytes (see below), but do not block the effect of cytokines on phagocytosis; indeed, they can promote it. Thus the binding of IFN- γ and subsequent expression of HLA-DR molecules and Fc receptors may be increased by low-dose steroids. However, the function of polymorphs is resistant to levels of steroids achievable pharmacologically, as judged by chemotaxis, phagocytosis and cytotoxicity.

Cytokine synthesis is inhibited

Studies in vitro have shown that physiological and pharmacological concentrations of steroids inhibit synthesis of cytokines but have little effect on their function. More impressively, after in vivo administration, reduced production of IL-1, -2, -4, -6 and -10, TNF- α and IFN- γ has been

demonstrated. Several different mechanisms may be involved: (1) attachment to potential glucocorticoid response elements in the promoter region of the cytokine genes (IL-4, -6 and -10), (2) direct binding, which antagonizes transcription-activating factors for IL-2, IL-8 and TNF- α , or (3) accelerating breakdown of mRNA (IL-1 and -3). The major consequences of this are inhibition of T-cell activation, both TH1 and TH2 cells of the CD4 subpopulation being similarly affected, and inhibition of cells of the monocyte/ macrophage system.

Cyclophosphamide acts by covalent alkylation

Together with chlorambucil, cyclophosphamide belongs to the group of immunomodulatory drugs which act by covalent alkylation of other molecules. Cyclophosphamide has no alkylating ability if self, but many of its metabolites are active, each having two active sites to effect the cross-linking of DNA strands, thereby interfering with strand separation during replication. The main side-effect is marrow toxicity, and so leucopenia must be monitored.

Both T- and B-cell functions are affected

Cyclophosphamide mainly affects lymphocyte numbers and function, particularly after low-dose daily oral therapy. Polymorphonuclear cell numbers may remain relatively unchanged. Low-dose oral therapy may have greater impact on cell-mediated responses, and bolus intermittent treatment more effect on antibody production. In both humans and experimental animals, after a low-dose bolus (600 mg/m² body surface area), numbers of B lymphocytes are reduced more than T cells and, among T-cell subsets, CD8 more than CD4; however, with higher dosage, all cell types are reduced similarly. Experimental studies have shown that this differential effect of low-dose depletion of CD8 cells shows a paradoxical increase in some CD4-controlled functions, such as antibody production. Evidence that low-dose cyclophosphamide has corresponding clinical relevance in humans remains equivocal.

As cyclophosphamide interferes with both B- and T-cell function, it is effective in controlling both antibody-mediated and cell-mediated immune responses in experimental animals and humans, and thus has a major role in the management of both autoantibody-mediated disease and allograft rejection.

Azathioprine

This drug, which is converted rapidly and non-enzymatically to 6-mercaptopurine *in vivo*, exerts its effect, after metabolism to thioinosinic acid, by competitive inhibition of purine metabolism and by incorporation into DNA as a fraudulent base. Its main effects are thus on DNA synthesis. Unlike cyclophosphamide, which is cytotoxic, azathioprine is cytostatic and is active only on dividing cells, exerting maximal effect if given soon after antigenic challenge. Allopurinol, which inhibits xanthine oxidase, increases the effective dose of azathioprine fourfold, and so if allopurinol is otherwise clinically essential, for example to treat gout, the dose of azathioprine should be reduced by 25%.

T- and B-cell numbers are reduced

Azathioprine is moderately immunosuppressive and produces modest reductions in both T and B cells after prolonged oral therapy at 2-3 mg/kg/day. Both K and NK cell activity appear to be specifically suppressed after its use. Humoral immunity and delayed hypersensitivity are not affected

at doses given clinically, although there is a reduction in mitogenic responses to pokeweed mitogen in lymphocytes taken from patients receiving the drug.

Mycophenolate mofetil

This drug was developed to target selectively the final stage of purine synthesis, along a pathway used specifically by lymphocytes proliferating in response to antigenic challenge. Thus, unlike nucleoside analogues such as azathioprine, it does not inhibit DNA repair enzymes or incorporate fraudulent purine analogues into DNA. Mycophenolate is rapidly hydrolysed in vivo to the active metabolite, mycophenolic acid.

Lymphocyte proliferation is blocked

Mycophenolate blocks both T- and B-cell proliferative responses in doses that appear to have no effects on other cell types. It also inhibits glycosylation of adhesion molecules involved in leucocyte traffic to endothelial cells, thus restricting amplification of inflammatory injury.

Methotrexate

A structural analogue of folic acid, this blocks folic acid dependent synthetic pathways essential for DNA synthesis.

Immunoglobulin synthesis is reduced after prolonged treatment

Several reports note reduction in immunoglobulin synthesis, with significantly lowered levels of all isotypes after three months of treatment. No consistent change has been noted in T-cell subsets, in either the short or long term, or the function of the monocyte/macrophage system. However, inhibition of dihydrofolate reductase involved in purine synthesis releases adenosine, which is a powerful inhibitor of activated polymorphonuclear leucocytes, hence methotrexate is anti-inflammatory. Other effects of methotrexate on inflammation may be mediated by its inhibitory effect on arachidonic acid metabolism. More anti-inflammatory activity such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), without affecting immune cell function or immunoglobulin synthesis.

Cyclosporine, tacrolimus (FK506) and rapamycin

These three drugs have complicated effects on T-cell signaling and hence T-cell functions. They all bind to a class of cytoplasmic proteins (named immunophilins) having peptidyl poly isomerase (rotamase) activity, which they inhibit. Immunophilins are believed to have a critical role in transducing signals from cell surface to cell nucleus.

Cyclosporine binds to one family of immunophilins, cyclophilins, whereas tacrolimus and rapamycin bind to the FK binding proteins. The cyclosporine-cyclophilins complex targets a serine threonine phosphatase called calcineurin, as does the tacrolimus – Fk binding protein complex. Both inhibit signal transduction pathways which characteristically produce an increase in intracellular free calcium, and inhibit transcriptional activation of cytokines and other genes essential for T-cell proliferation and function. Rapamycin on the other hand, blocks T-cell proliferation by a different

mechanism, through inhibition of IL-2-dependent signal transduction pathways which function independently of calcium concentration and do not affect cytokine gene transcription (Figure-2).

T-cell proliferation is inhibited

Cyclosporin has a marked inhibitory effect on early events of T-cell proliferation indeed by mixed lymphocyte reactions, concanavalin A or phytohaemagglutinin. It has a specific effect on B cells, inhibiting antiglobulin-driven proliferative responses but not those due to stimulation with lipopolysaccharide. Antigen-presentation by monocytes and Langerhans' cell is also affected. Thus the effect of cyclosporine, while profound on T cells extends to other cells of the immune system. It is believed that tacrolimus has a mode of action similar to that of cyclosporine, albeit by attachment to a different immunophilin. However, rapamycin also affects cells of non-haemopoietic origin; for example, it inhibits proliferation of vascular smooth muscle cells after balloon catheter injury and may then be useful in preventing restenosis after angioplasty. Also, because it inhibits T-lymphocyte proliferation at a later stage than cyclosporine or tacrolimus, it may be used synergistically with these agents, or as an alternative, in conditions refractory to the use of one or the other.

NUTRITION AND IMMUNE RESPONSES

The relationship between nutrition and resistance to infection has been suggested by historical accounts of famine and pestilence, clinical observations, and epidemiological data. Generally, nutrient deficiencies are associated with impaired immune responses. The five aspects of immunity most consistently affected by malnutrition are cell-mediated immunity, phagocyte function, the complement system, secretory antibody, and cytokine production. Worldwide, undernutrition is the commonest cause of immunodeficiency.

Economically underprivileged countries have a high prevalence of nutritional deficiencies, as do poor segments of society in many industrialized countries. In addition, many individuals show a nutrition problem secondary to another primary systemic disorder: patients with cancer, chronic renal disease, burns, multiple trauma and chronic infection show a high prevalence of malnutrition. Paradoxically, obesity and excess intake of nutrients are also associated with reduced immune responses.

Malnutrition and infection

Infection and malnutrition usually aggravate each other. However, nutrition does not affect all infections equally: the clinical course and final outcome of pneumonia, diarrhea, measles and tuberculosis are affected adversely by nutritional deficiency; for some infections (e.g. tetanus and viral encephalitis), the effect of nutritional deficiency is minimal; for others (e.g. influenza virus and human immunodeficiency virus), nutrition exerts a moderate influence.

There are many factors that predispose to development of infection in the malnourished individual, including poor sanitation, contaminated food and water, lack of nutritional and health knowledge, illiteracy and overcrowding.

Lymphoid tissues

Lymphoid tissues are very vulnerable to the damaging effects of malnutrition. The extent and severity of lymphoid dysfunction caused by nutrient deficiencies depend upon several factors, including the rate of cell proliferation, the amount and rate of protein synthesis and the role of individual nutrients in critical metabolic pathways. Numerous enzymes with key roles in immune processes require zinc, iron, vitamin B₆ and other micronutrients in order to function.

Lymphoid atrophy is a prominent morphological feature of malnutrition. The thymus in particular, is a sensitive barometer in young children and the profound reduction in weight and size of the organ in several malnourished subjects has been termed 'nutritional thymectomy'. Histologically, the lobular architecture is ill-defined, there is a loss of corticomedullary demarcation, and there are fewer lymphoid cells. Hassall's corpuscles are enlarged and degenerate; some may be calcified. Atrophy is observed in the thymus-dependent periarteriolar areas of the spleen and in the paracortical section of the lymph nodes.

Protein-energy malnutrition (PEM)

Moderate/severe malnutrition is associated with a significant reduction in cell-mediated immunity, indicated by a reduced number of CD4⁺ T-helper cells, and lower CD4⁺/CD8⁺ ratio (Figure-3). Co-culture experiments indicate a reduction in T-cell help available to B lymphocytes. Lymphocyte proliferative responses to mitogen are decreased. The immaturity of circulating T cells is reflected in increased leucocyte deoxynucleotidyl transferase activity. Reduced thymulin activity may underlie these changes in T-cell number and function. There is a reduction in the secretory IgA antibody response to common vaccine antigens, which may contribute to a higher incidence of mucosal infections.

Phagocytosis is affected in PEM. Opsonization is decreased, largely because of a reduction in levels of various complement components: C3, C5 and Factor B. whereas ingestion of microorganisms is intact in PEM, the ability of phagocytes to kill intracellular organisms is impaired. The production of certain cytokines, such as IL-2 and TNF, is decreased.

Some innate mechanisms of immunity are also affected by nutrition. The production of lysozyme is slightly decreased. A larger number of bacteria bind to epithelial cells of malnourished subjects; wound healing is impaired. There are very few data on the quality and quantity of mucus produced in PEM.

Individual nutrients

The profound effect of *zinc* deprivation on immune responses has been documented extensively. There is a reduction in delayed cutaneous hypersensitivity, lower CD4⁺/CD8⁺ ratios and T-cell dysfunction. A striking and pathognomonic feature of zinc deficiency is reduction in the activity of serum thymulin, (a nonapeptide that contains zinc as an integral part of its molecule) and lymphoid atrophy.

Intergeneration effect of zinc on immunity: an even more surprising finding is the effect in mice of zinc deficiency in pregnancy. Even the third generation progeny have impaired antibody responses as shown by diminished plaque-forming cells of IgM (Figure-4).

Iron is a double-edged sword: it is required by most microorganisms for their growth, while iron-dependent enzymes have crucial roles in lymphocyte and phagocyte function. Thus iron deficiency is generally associated with reduced ability of neutrophils to kill bacteria and fungi, decreased lymphocyte response to mitogens and antigens, and impaired NK cell activity.

Selenium and copper are also important for immune responses. An exciting recent observation indicated that viruses can mutate and show altered virulence in malnourished hosts they infect. Coxsackie virus recovered from selenium-deficient mice produced heightened myocardial damage; there were six nucleotide changes between the virulent input strain and the virulent virus recovered from selenium-deficient animals.

The clinical counterpart of Coxsackie myocarditis and nutritional deficiency is Keshan disease, which was endemic in some parts of China. Selenium supplementation has virtually eradicated this condition.

Vitamin A deficiency alters epithelial structure, leading to metaplasia and increased binding of bacteria. There is a reduction in the numbers of certain lymphocyte subsets and in the response to mitogen.

Vitamin supplementation is of value in preventing complication of severe measles and reducing morality from this disease.

Vitamin B₆ and folate deficiencies reduce cell-mediated immunity, particularly lymphocyte proliferation responses, and also impaired antibody production.

Obesity and excessive intake of nutrients

Obese subject and animals show alternation in various immune responses, including cytotoxicity, NK activity and the ability of phagocytes to kill ingested bacteria and fungi. Altered levels of some micronutrients, lipids and hormones may explain these immunological changes.

Some nutrients given in moderate excess enhance selected aspects of immune response, particularly cell-mediated immunity. These include vitamin E, vitamin A, zinc and selenium. However, for most nutrients, there is an upper limit of intake beyond which immune responses are impaired.

Clinical implications

There are exciting new possibilities for nutritional intervention for both primary and secondary prevention of infection in high-risk groups. Hospital inpatients who are malnourished are at high risk of complicated opportunistic infection. Nutrient-enriched feeding formulas enhance immunity and reduce risk of complications such as sepsis and poor wound-healing. In the elderly, respiratory infection is a common cause of illness, modest amounts of micronutrient supplements improve immune responses and, more significantly, reduce the incidence of respiratory infections and

antibiotic usage. Furthermore, post vaccination immune responses are higher in subjects given nutritional supplements than in untreated controls.

Probiotics. in both clinical and veterinary medicine, the value of probiotics is being recognized. These 'desirable' bacteria such as *Lactobacillus acidophilus*, *L.casei*, cocci such as *Enterococcus faecium* and bifidobacteria are given orally to replace or increase their presence in the gut microflora.

Benefits to health and immunity come from the 'barrier effect' in the gut, production of bacteriocidins and by altering the local immune response via a change in cytokine profile in the gut mucosa and increased antibody production.

It is still an open question as to how the immunological changes translate into improved health but that effect has been shown quite clearly in children with AIDS.

AIDS

Human immunodeficiency virus (HIV) causes AIDS and is transmitted sexually, in blood or blood products, and perinatally. There are two main variants, HIV-1 and HIV-2. HIV-2 is endemic in West Africa and appears to be less pathogenic.

More than 80% of people infected with HIV live in developing countries and spread is 80% by the sexual route (70% vaginal; 10% anal). The World Health Organization (WHO) estimates that, by the year 2000, the cumulative total infected will reach 30 million, with 99% of all infections in developing countries and 2 million people dying of AIDS each year.

The virus

HIV is single stranded diploid RNA virus 100-120 nm in diameter (Figure-5). Its basic gene structure has *gag* (core protein), *pol* (polmerse/reverse transcriptase) and *env* (envelope protein) genes. Additional genes regulate viral protein synthesis. CD4 antigen is the receptor for the virus; it is present on CD4⁺ T lymphocytes and cells of the monocyte/macrophage lineage. Viral gp120 binds to CD4, but chemokine receptors are involved in the subsequent gp41-mediated fusion and internalization.

Immune dysfunction

There is wide immune dysfunction, with immune depression within a milieu of immune activation, resulting from direct effects of HIV and from the depletion and functional impairment of the CD4⁺ T-cell subset over time. How HIV kills its target cells is not well understood; several different mechanisms have been proposed, including accumulation of RNA and unintegrated DNA in the cell cytoplasm, and intracellular binding of CD4 and gp120. Infected cells may bind to uninfected cells by gp120-CD4 linkages, with multinucleate giant cell and syncytium formation. Gp120 bound to the surface of uninfected CD4⁺ T cells also makes them vulnerable to antibody-dependent cell-mediated cytotoxicity (ADCC), while infected cells may be killed by gp120-specific cytotoxic T cells. HIV proteins may act as superantigens, resulting in vast expansion and then exhaustive depletion of cells.

In addition, HIV may induce T-cell apoptosis and viral budding may lead to cell-membrane weakening and lysis.

The spectrum of immune dysfunction is characterized by depletion of the CD4⁺ T-cell subset and decreased responses to antigens, mitogens, alloantigens and anti-CD3 antibody, associated with decreased IL-2 production and other changes in cytokine production. Eventually, there is loss of HIV-specific cytotoxic T-cell responses and certain antigen-presenting cell functions. There is an increase in activated and unresponsive CD8⁺ T cells, increased β_2 -microglobulin and neopterin in serum, polyclonal B-cell activation with B cells refractory to T-cell-independent B-cell activators, and an increase in autoantibodies and immune complexes.

Modeling of the plasma virus and CD4⁺ T-cell responses to antiviral therapy suggests that the average half-life of the virus and infected cells in the circulation is less than two days. 10^9 - 10^{10} viruses are released from infected cells and similar numbers of new cells are infected and die daily.

Natural history

Primary infection with HIV may be accompanied by transient illness similar to glandular fever, with malaise, muscle pains, swollen lymph nodes, sore throat and rash. There is transient depletion of peripheral CD4⁺ T cells, expansion of CD8⁺ T cells and high plasma levels of HIV (Figure-6). In 2-6 weeks, antibodies to core and surface proteins can be detected by enzyme-linked immunoassays. A chronic infection ensues without illness, but about 33% of patients have swollen lymph nodes. Fifty percent of those infected develop AID within 9-10 years.

Later in infection, non-specific constitutional symptoms such as fevers, night sweats, diarrhoea and weight loss occur, together with 'minor' conditions that largely affect the mucous membranes and skin: for example, oral candidiasis (thrush), shingles, recurrent anogenital herpes simplex and a variety of skin infections. These conditions often signal the development of serious opportunistic infections and tumors, which constitute AIDS when the CD4⁺ T cell count is, usually, below 200/ul (Figure-6).

Kaposi's sarcoma, a multifocal tumor of endothelial cell (Figure-7), is the commonest tumor. Widespread skin, mucus-membrane, visceral (gut and lungs) and lymphnode disease occurs. Infection with human herpes virus 8 (HIV8) is associated with the development of the tumor B-cell lymphomas also occur, affecting the brain, gut and bone marrow.

Most of the opportunistic infections are due to reactivation of latent organisms in the host or, in some cases, ubiquitous organisms to which we are continually exposed. They are difficult to diagnose and treatment often suppresses rather than eradicates them. Relapses are common and continuous suppressive or maintenance treatment is necessary, using drugs that cause side-effects.

Three main organ systems are affected: the respiratory system, gastrointestinal tract and nervous system. Pneumonia is common and *Pneumocystis carinii* is the commonest infection (Figure-7), but bacterial infections, including *Mycobacterium tuberculosis*, and fungal infections also occur. Discomfort on swallowing is usually caused by candidiasis (thrush), but cytomegalovirus can cause oesophageal ulceration. Protozoa (*cryptosporidium* and *microsporidia*) are the commonest pathogens isolated in patients with diarrhoea and weight loss (Figure-7), but enteric bacteria such as *Salmonella* and *Campylobacter* may also be found.

Neurological complications in AIDS are due to direct effects of HIV infection, opportunistic infections or lymphoma. AIDD-related dementia once affected between 10% and 40% of patients with other manifestations of AIDS, but, with more effective antiviral treatment, has become less common. Spinal cord and peripheral nerve disease also occur. Toxoplasmosis, a protozoal, causes cysts in the brain and neurological deficit (Figure-7). *Cryptococcus neoformans* is fungus which causes meningitis. Cytomegalovirus may cause inflammation of the retinae, brain and spinal cord and its nerve roots, and a polyomavirus (JC virus) which infects oligodendrocytes in the brain produces a rapidly fatal demyelinating disease – progressive multifocal leucoencephalopathy.

Antiviral treatments

In 1987, zidovudine (AZ) was licensed as the first nucleoside analogue reverse transcriptase inhibitor (NRTI), to be used in HIV infection. There have been considerable advance since then, with the development of other NRTIs and non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (Figure-5).

Zidovudine monotherapy in patients with advanced disease reduces the short-term morality and progression of disease. Early in infection, clinical benefit is small and transient, with no improvement in survival. As a result, combinations of two or more drugs have been used, with the aims of enhancing efficiency through additive or synergistic effects and delaying the emergence of resistance by slowing the rate of mutation of the RT gene or by conferring mutations that might reverse resistance or lead to less competent viruses. Combination of two NRTIs reduces the rate of progression of AIDS and death by approximately 40% over 1-3 years compared with monotherapy. Combinations of NRTIs and protease inhibitors have also been clinically effective. The use of other multiple combinations of NRTIs, NNRTIs and protease inhibitors produces promising antiviral effects, together with impressive short-term CD4⁺ T-cell increases, which may provide additional clinical benefits.

The optimal time to start therapy remains unclear, but most physicians act on a repeatedly low CD4 count of 200-400 cells/nl⁻¹ and in all patients who are symptomatic. Serum HIV RNA levels also influence this decision. The cost even of monotherapy is prohibitive for most developing countries. As no cure or vaccine is currently available, our main weapon is prevention through health education and control of infection.

Effects of glucocorticoids on circulating leucocytes

Cell type	Hour after injection		
	0	6	24
Neutrophils	400	10000	4000
Lymphocytes	200	500	2000
Eosinophils	400	100	400
Monocytes	300	50	300
Basophils	100	0	100

Figure-1 Effect of a doses of glucocorticoid (40 mg/kg), given once at time 0, on circulating human leucocyte number (per mm³).

Cyclosporin, tacrolimus and rapamycin

	cyclosporin	tacrolimus	rapamycin
lymphokine secretion (IL-2, -3, -4, -6, GM-CSF, IFN γ)	↓	↓	– or ↑
IL-2 receptor expression	↓	↓	–
inhibition of response to IL-2	–	–	+

Figure-2: Differential effects of cyclosporine, tacrolimus and rapamycin immunophilins on cytokine activity.

Lymphocyte subsets

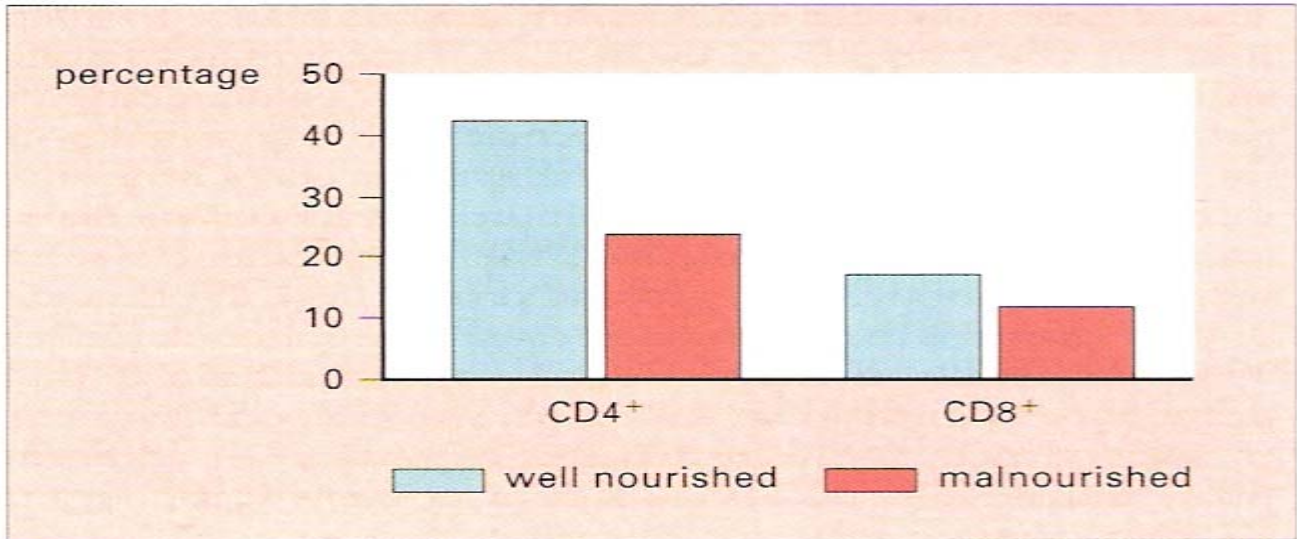


Figure-3 Lymphocyte subsets in children with protein-energy malnutrition and in well-nourished controls.

Intergeneration effects of Zn deficiency on immunity

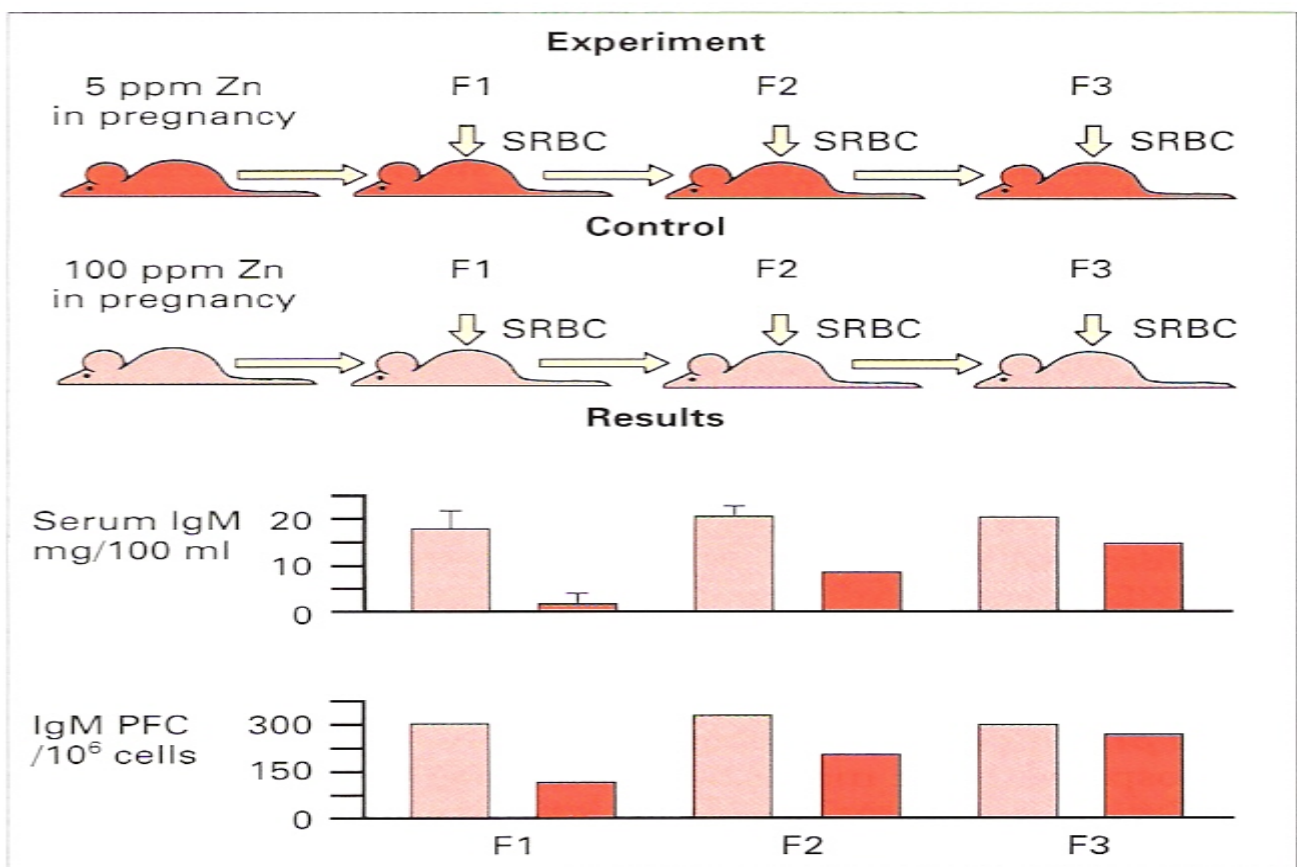


Figure-4 An experimental group of animals was fed a Zn-deficient diet (5 ppm Zn) during the later two-thirds of pregnancy and a control group was fed a Zn-adequate diet (100 ppm Zn) during the same period. The former regime reduced serum Zn to 60-70% of control values. F1, F2 and F3 generations were fed sufficient Zn throughout. Both the PFC response and serum concentration of IgM were assessed at 6 weeks. Results showed that both were low in at least three generations of offspring.

Human immunodeficiency virus and its life cycle

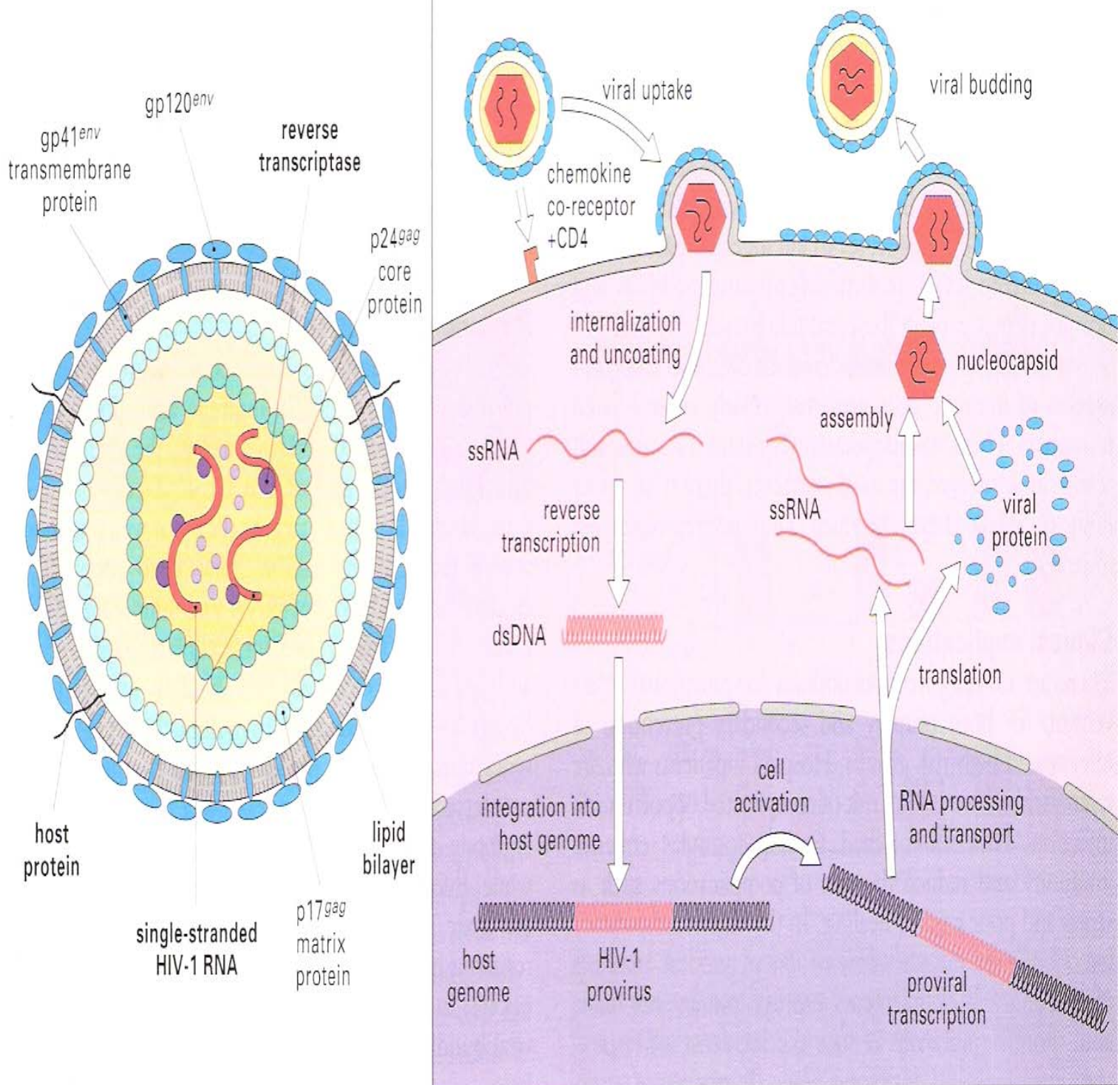


Figure-5 After uncrating, reverse transcription of viral RNA results in the production of double-stranded DNA. This is inserted into the host genome as the HIV provirus, by a virally coded integrase enzyme. Cell activation leads to transcription and the production of viral mRNAs. Structural proteins are produced and assembled. Free HIV viruses are produced by viral budding from the host cell, after which further internal assembly occurs with the cleavage of a large precursor core protein into the small core protein components by a virally coded protease enzyme, producing mature virus particles.

Natural history of HIV

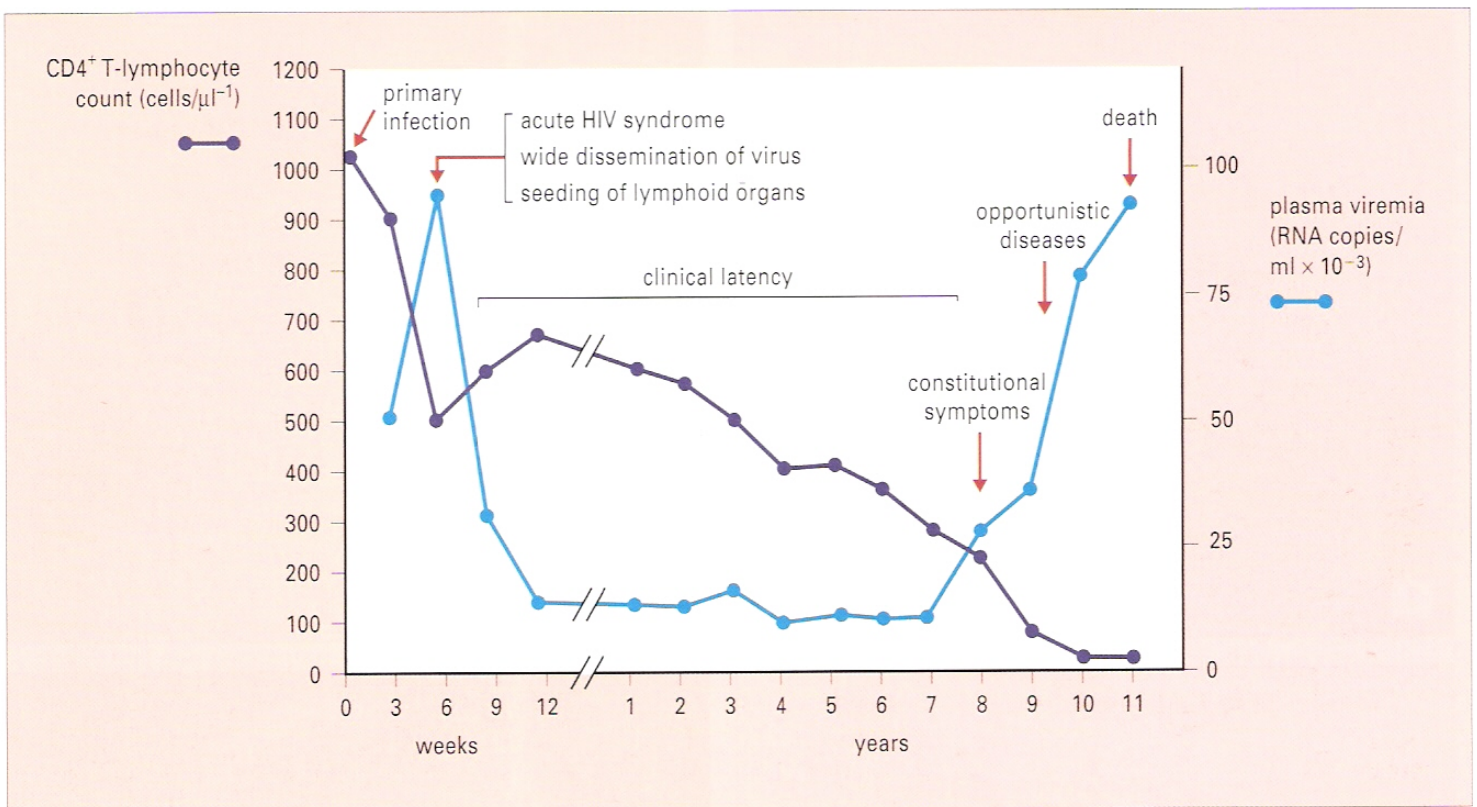


Figure-6: A typical course of HIV infection, courtesy of Dr. A.S. Fauci.

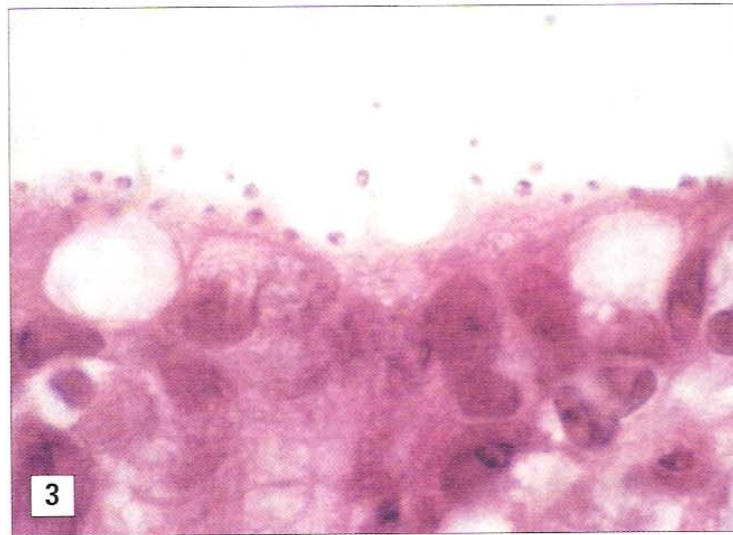
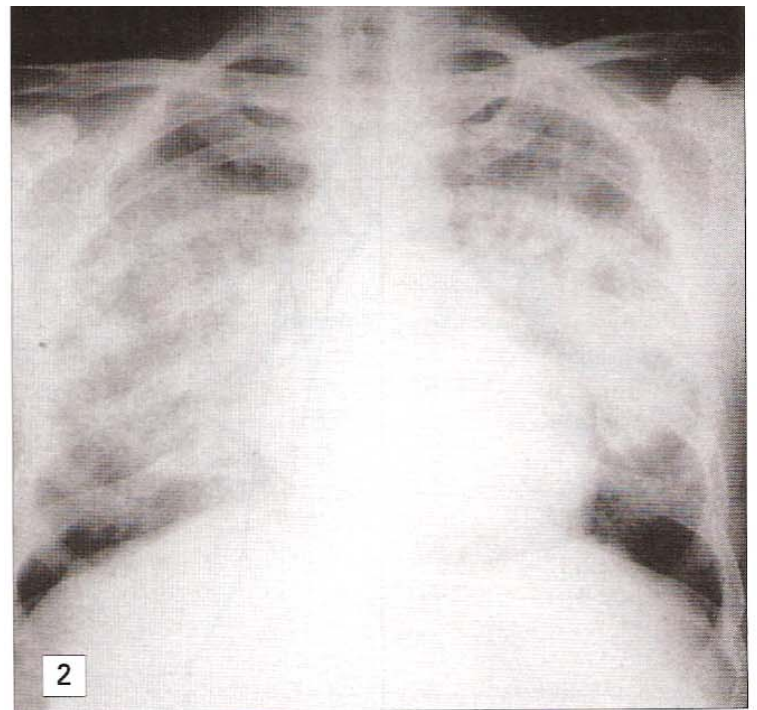


Figure-7: Common features of AIDS. (1) Multiple Kaposi's sarcoma lesions on the chest and abdomen. (2) Chest radiograph of a patient with *Pneumocystis carinii* pneumonia, showing bilateral interstitial shadowing. (3) Small bowel biopsy from a patient with diarrhoea caused by *Cryptosporidium*, showing intermediate forms of cryptosporidia (small pink dots) on the surface of the mucosa. (4) Computed tomography (CT) scan of the head of a patient with cerebral toxoplasmosis. The patient presented with a history of fits and weakness of the left arm and leg. Injection of contrast revealed a ring-enhancing lesion in the right hemisphere, with surrounding oedema (dark area).

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