Immuno deficiency

Pages with reference to book, From 93 To 98

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Immunodeficiency

The world is now faced with the managernent of patients who are immunodefIcient because of several different factors which contribute to a poor soil or terrain (Table 1).

Table I

Factors Influencing the Terrain and Contributing to Poor Resistance against Disease.

Cellular Immunity
Humoral Immunity
Phagocytosis
HLA Antigens
Malnutrition
Vascular Insufficiency
Disseminated Neoplasia
Drugs
Autoimmunity
Atopy
Ageing

Let us study these factors which are responsible for poor resistance against disease.

Factors Influencing the Terrain (Table I)

1) Cellular and Humoral Immunity.

An antigen that penetrates the body's external defences (skin, mucous membranes, cilia) will encounter two populations of circulating lymphocytes. These two systems, responsible for cellular and for circulating immunity, are the cornerstones of an elaborate and powerful defence system.

T-cells are responsible for cellular immunity. They carry memory, can affect B-cells, reject grafts, recognise cancer, and prevent viral and fungal infections. Their chemical mediators are lymphokines and interleukins and they are involved in the production of interferons. T-cells are particularly involved in the defence against organisms that have an intracellular phase, for instance viruses, mycobacteria, Brucella, and fungi. There are now simplified techniques for recognising T cells and their subsets, and HLA-DR antigen in peripheral blood smears by immunoalkaline phosphatase staining. This lends itself

to mass screening of circulating lymphocyte sub-populations, as, for example, in blood donors.[1]

B-cells are responsible for humoral immunity. They produce five major immunoglobulins and a variety of circulating antibodies. These are responsible for the lysis of antigen by fixing complement, opsonization of bacteria and the neutralization of their products. Deficiencies of B-cells cause increased susceptibility to infection by common bacteria.

Phagocytosis

Phagocytes reach the site of invasion by chemotaxis where they ingest and kill the foreign organism. Impairment of function includes poor chemotaxis, intrinsic cellular defects, abnormal opsonization and neutropenia.

Chemotaxis:can be visualized by several in vitro techniques. Poor leucocyte be locomotion may associated with inhibitors, and blocking factors, deficiencies in complement.

Intrinsic cellular defects may render phagocytes important as in the chronic granulomatous disease of childhood.

Opsonization involves the preparation of bacteria for digestion by phagocytes through the coating of bacteria by the third component of complement (C3b). Opsonic activity requires intact receptor sites, and neutrophil attachment to the organism occurs at the Fab site. Patients with various types of C3b deficiency have poor opsonic activity and are more prone to infections.

Neuz'ropenia may be the result of a variety of causes amongst which are drugs, neoplasia, infections, connective tissue diseases and bypersplenism (Table II).

Table II

Causes of Neutropenia.

DRUGS	HYPERSPLENISM
Aminopyrine	Hepatic cirrhosis
Phenylbutazone	Myelofibrosis
Methyldopa	Autoimmune disease
Phenothiazines	Gaucher's disease
Chloramphenicol	Felty's syndrome
Thiouracil	INFECTIONS
Gold	Malaria
Chlorpropamide	Viral hepatitis
Procainamide	Typhoid fever
Quinidine	Infectious mononucleosis
Chloroquine	
Penicillamine	
Diphenylhydantoin	MISCELLANEOUS
Cyclophosphamide	Cyclic neutropenia
Nitrogen Mustard	Bone marrow replacement
NEOPLASIA	Congenital neutropenia
Leukaemia	Nutritional deficiency
Lymphoma	Systemic lupus erythematosus
Carcinomatosis	Rheumatoid arthritis
Lymphosarcoma	Polyarteritis nodosa
DEFECTIVE PHAGO–CYTOSIS	Extra-corporeal circulation
Chronic granulomatous disease	INADEQUATE CHEMOTAXIS
Sickle-cell anaemia	Lazy leucocyte syndrome
Poor opsonisation	Chediak-Higashi syndrome
Lysosomal enzyme deficiency	
Glucose 6 P-D deficiency	

HLA Antigens

The human leucocyte system of antigens are on the membrane of all nucleated cells and platelets and are inherited on a pair of autosomal chromosomes. Four HLA antigens are found in any individual, two

derived from each of two closely linked genetic loci. These tissue antigens are a most important constituent of the terrain and there is now increasing recognition of associations between particular HLA antigens and diseases, some of which are highly significant. Examples include the possession of HLA B27 predisposing the individual to sero-negative arthritis and joint complications of inflammatory bowel disease, and possession of DRw3 which increases the likelihood of, amongst others, some 'autoim mune disorders' including thyroiditis, Addison's disease, and gluten-sensitive enteropathy (Table III).

Table III

HLA-Associated Disorders.

	Clinical Disorder	
HLA	Ophthalmic	Other
B27	Acute Anterior Uveitis Ankylosing Spondylitis Behcet's Disease Reiter's Disease Psoriatic arthropathy Juvenile rheumatoid arthritis	Crohn's Arthritis Ulcerative colitis arthritis Yersinia & Salmonella Arthritis Levamisole toxicity
B7	Ankylosing spondylitis in black Americans	
B8 ; DHW3	Myasthenia Gravis Graves' Disease & relapse following carbimazole Sjogren's syndrome Juvenile diabetic retinopathy	Thyroiditis Addison's Disease Coeliac Disease Dermatitis herpetiformis Chronic active hepatitis Idiopathic membranous nephropathy
B8 ; DHW2	Systemic Lupus Erythematosus	
B2 & B9		Acute lymphoblastic leukaemia (long survivors)
B13, B17, CW6		Psoriasis (without arthropathy)
A3; B7; B18; DWL; DHW3	Multiple Sclerosis	
A9		Transitional cell carcinoma of bladder Buerger's disease
B8; BW15; DW2; DW4		Insulin-dependent diabetes mellitus
A3; B14		Haemochromatosis
A1; A11; B5; BW15	Hodgkin's lymphoma	
B8	Sarcoid arthritis and Uveitis with Erythema nodosum Giant cell arteritis Polymyositis & juvenile dermatomyositis Systemic sclerosis	Hodgkin's (long survivors) Hypogonadism Schizophrenia
DR5		Kaposi's Sarcoma AIDS

Other factors influencing the terrain

Malnutrition, ischaemia, disseminated neoplasia, drugs and chemotherapy may all profoundly alter the soil and contribute to the poor resistance of the patient. Splenectomy may lead to increased susceptibility of the individval to certain infections, particularly, pneumococcal and streptococcal (Table IV).

Table IV

Conditions in Which Impaired Defences Lead to Infections.

Defences	Diabetes Mellitus	Alcoholism + Hepatic Cirrhosis	Drug Addiction	Following Splenectomy
Polymorphs Phagocytosis Chemotaxis	 ± Impaired	 Leucopenia Impaired	 Normal	Impaired by underlying disease responsible for splenectomy
Cellular immunity	Impaired	T cell depression + increased null cells	? Impaired	Normal Impaired by any underlying disease, such as Hodgkin's Disease
B cells Immunoglobulins Antibodies	Normal	Polyclonal gammopathy when there is underlying liver disease	Polyclonal gammopathy	Impaired primary antibody response. Decreased IgM
Miscellaneous –Opsonins –Complement	 Normal Normal	 Impaired by underlying disease	 ? Abnormal	 Normal Normal
Other contributary factors	Vascular insufficiency Autonomic neuropathy	Vitamin deficiency Alcoholic cirrhosis	Autoinoculation Coma Hypoventilation Pulmonary oedema	Hodgkin's Disease Sickle Cell disease Thalassaemia Congenital spherocytosis Thrombocytopenic purpura
Infection	Staphylococcus aureus septicaemia & skin infections Monilia (Candida) albicans and other fungi E. coli urinary tract Gram-negative cholecystisis	Pneumococcal pneumonia Klebsiella pneumonia Anaerobic lung abscess Pulmonary tuberculosis E. coli septicaemia and peritonitis	S. aureus causing pyoderma, cellulitis endocarditis, osteomyelitis, septic arthritis Pneumococcal Pneumonia Tetanus HBSAg hepatitis Pyogenic sacroiliitis	Pneumococcal and streptococcal septicaemia Bacterial meningitis. There is not an increased incidence of viral infections

The patterns of opportunistic infections depend upon the mechanism of immunosuppression: thus, patients who have received organ transplants and subsequent immunosuppression may have poor cell-mediated immunity and be at risk of contracting Cytomegalovirus, pneumocystis, and disseminated Candida infections.[2] Those who have reduced humoral defence (e.g. Leukaemia patients) may be prone to Aspergillus, pseudomonas, Mycoplasma, and Salmonella infections, whilst those with poor macrophage function (e.g cystic fibrosis) may be especially liable to Staphylococcus and Pseudomonas infection.

Disorders With a Poor Terrain

Acquired Immuno-Deficiency Syndrome (AIDS)

This epidemic disorder is most commonly seen in promiscuous male homosexuals, haemophiliac, and drug addicts with poor cellular immunity. Numerous opportunistic infections are associated with weight loss, fever, diarrhoea, peripheral lymphadenopathy, lymphopenia, and Kaposi's sarcoma (Table V).

Table V
Percentage Frequency of Various Features of AIDS,

Features	% Frequency
Male	93
Pneumocystis) Pneumonia)	51
Kaposi sarcoma	26
Both of Above	8
Multiple Infections	15
Lymphomas	Frequent
Homosexuals	71
Drug Addicts	17
Haemophiliacs	0.7
Haitian	0.5
T4 : T8 Unity or Less	100
Lymphadenopathy) Fevers) Weight Loss) Diarrhoea)	Frequent
Alpha Interferon) Thymosin 1 α) in serum	High
Thrombocytopenia	Frequent
Mortality	70

There is an overall mortality of 70% and treatments have all been uniformly unsuccessful. There may be a genetic predisposition because an increased frequency of HLA-DR5 allotype has been noted in male homosexuals with the epidemic form of Kaposi's sarcoma.[3]
The immunologic pattern comprises 1-helper cell lymphopenia, an OKT4:OKT8 ratio reduced to less

than unity, cutaneous anergy, decreased natural killer (Nt) cells, decreased response to proliferative mitogens (phytohaemagglutinin, Concanavalin A, pokeweed), normal neutrophil function, and normal or increased levels of immunoglobulins. Many patients have an unusual acid-labile form of human leucocyte or alpha-interferon[4] and thymosin 1 serum levels may also be high.[5] It is hoped that HTLV III antibodies prove to be serological markers of the disease.

Kaposi's Sarcoma

Kaposi's sarcoma is a multifocal reticuloendothelial neoplasm which has attracted considerable attention in the last decade because of its high incidence in renal transplant recipients, immunosuppressed individuals and sick homosexuals. Kaposi[6] originally described pea-sized brownish-red to bluish-red skin nodules that first appeared on the soles and dorsum of the feet and later spread to the rest of the skin and ultimately to the gut, liver, and upper respiratory tract. His patients died within three years.

Homosexuals who engage in ano-genital intercourse with numerous partners have eleven times the risk of developing Kaposi's sarcoma than less promiscuous homosexuals. It occurs particularly in the passive partner receiving semen into the gastro-intestinal tract by rectum or by swallowing it. This suggests that an infectious agent in semen is transmitted or that semen ejaculated into a foreign environment causes an immunologic disturbance. About one half of patients with Kaposi's sarcoma belong to HLA-DR5 (normally only present in 25% of the population) and these patients have a particularly low level of T4 lymphocytes with a very low T4:T8 ratio, even below 0.5.

The immunological abnormalities found in the blood of such patients extend into the lymph nodes[7] T-suppressor cells invade the follicles of the node where they are normally absent and numbers of T helper cells are decreased. There is reduction of the T4:T8 ratio to less than unity. In addition there is B cell hyperplasia within the node and an increase in the number of fully differentiated B cells in the peripheral blood. The latter occur at the expense of the precursors and such polyclonal stimulation would be in keeping with, viral B cell activation in the absence of normal regulatory T cell influence.

The Cause of AIDS? [8-15]

French workers isolated lymphadenopathy associated virus (LAV) from a homosexual with pre-AIDS, and also found the same virus in fully-developed AIDS. This was soon followed by a report from the National Institutes of Health. Bethesda, of the isolation of a human T leukaemia retrovirus (HTLVIII) from 48 AIDS patients but from none of 115 healthy controls. The French LAV and American HTLVIII are probably the same retrovirus, which has a selective tropism for T-helper cells. It is likely that there are several co-factors including, of course, T helper cell ablation, B cell overactivity, CMV irnmunosup. pression, genetic HLA susceptibility, and semen (Fig. 1).

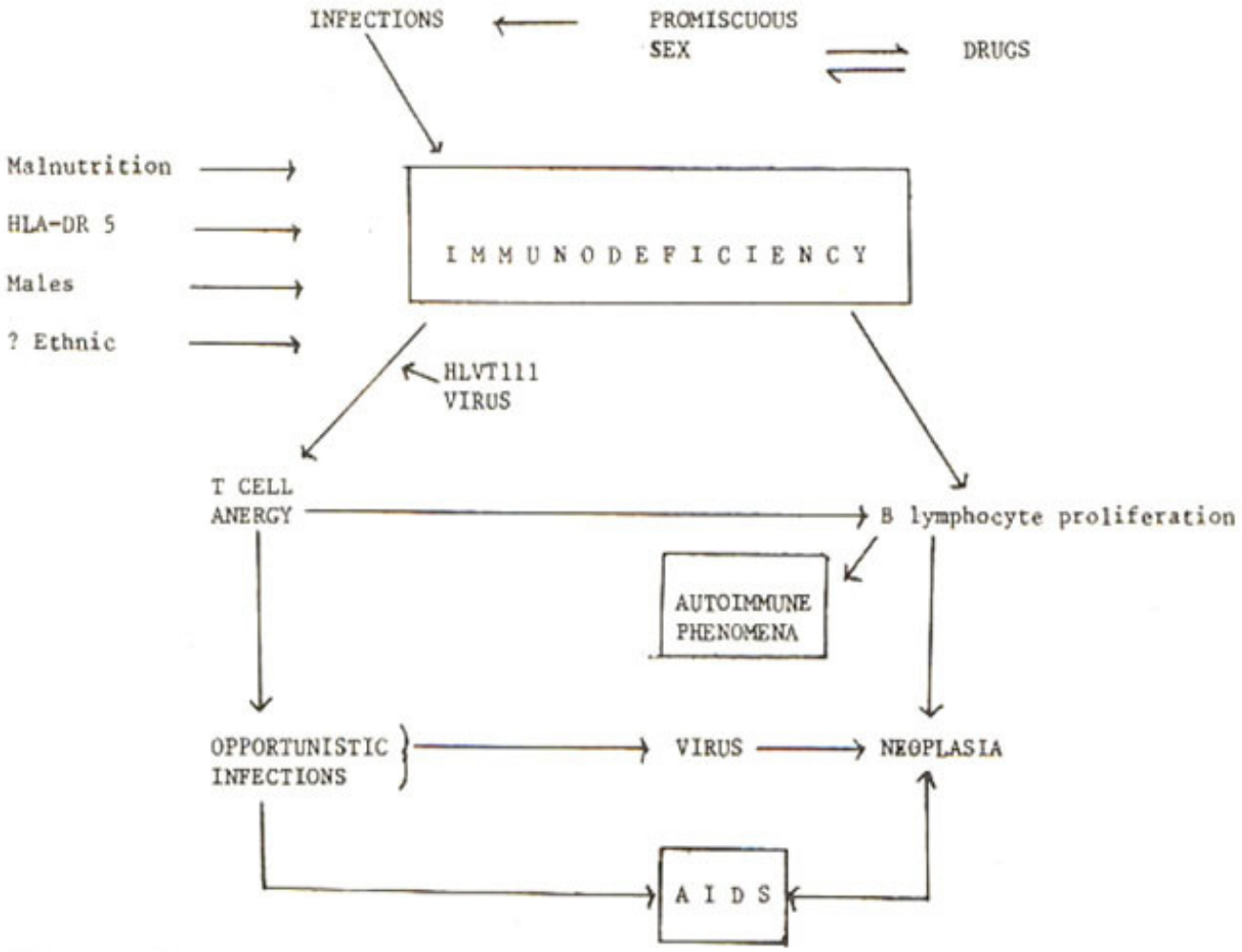

Fig. 1. Factors Contributing to Acquired Immunodeficiency Syndrome (AIDS).

IgG antibodies to LAY were found in 75% of patients with AIDS, 90% with lyrnphadenopathy syndrome, 18% of homosexual men without lymphadenopathy and 0.3% of unselective blood donors. The presence of HTLV-III serum antibodies is most strongly associated with sexual exposure to men in the United States and to anai receptive intercourse.

Toxoplasmosis[16]

Acute toxoplasma encephatitis is difficult to diagnose if it is not suspected, and particularly so when toxoplasma 1gM antibodies are not detected or when there is no rise in dye-test titres. It is recognised in homosexuals, drug addicts and in Haitians, but it also occurs in otherwise healthy individuals, who develop immunodeficiency,unaccountably due to ablation of the helper T cell subset. There is a profound lymphopenia, and spinal fluid examination may reveal high protein and low glucose levels.

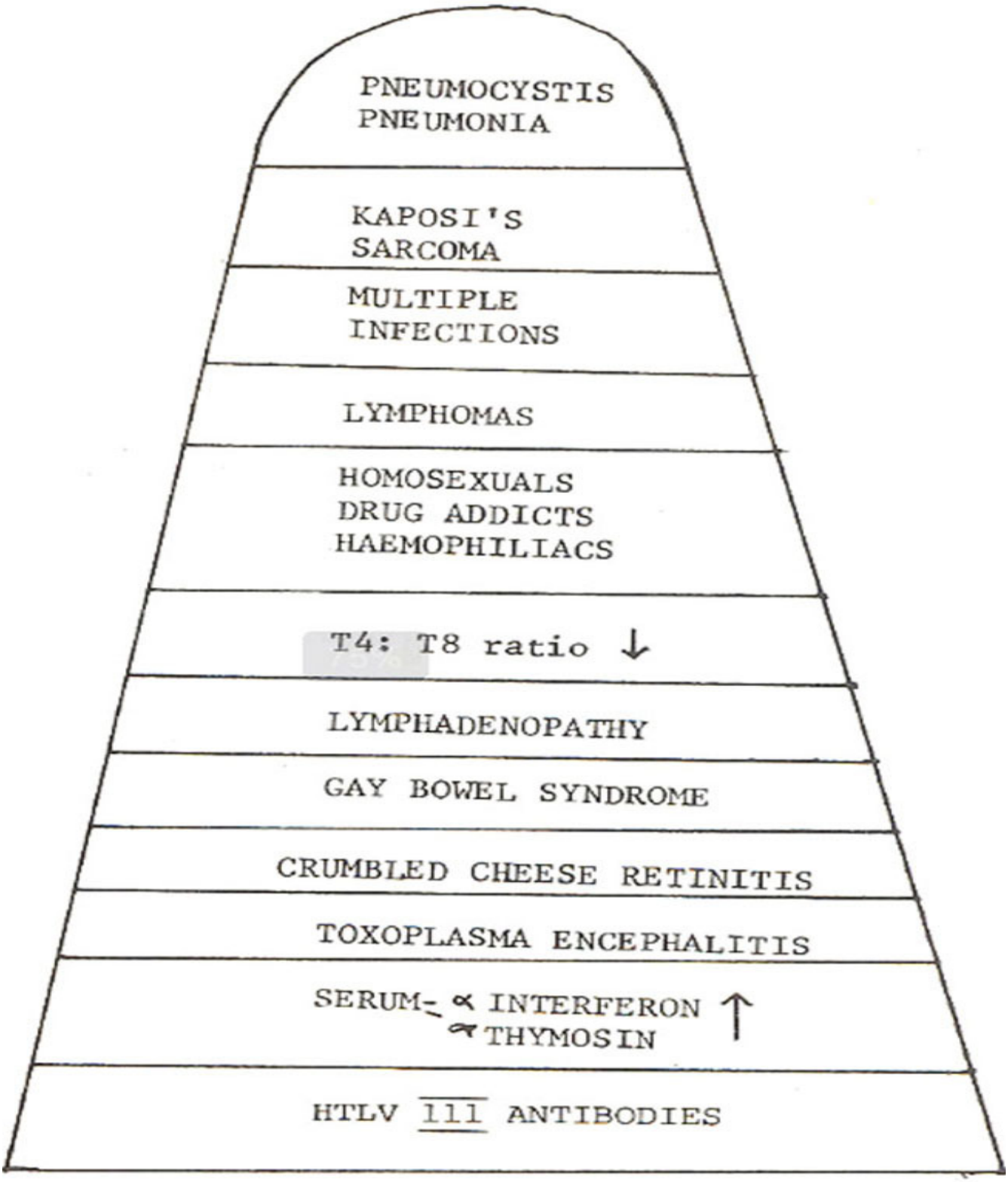

Fig. 2. AIDS is an iceberg syndrome.

Pnewnococcal Bacteraemia[17]
This is associated with pre-existing diseases:-
(a) Disorders of the respiratory system, in- clu ding heavy smoking, steroid-treated asthma, chronic

bronchitis, recurrent pneuni onia and cardiovascular disease.
(b) Disorders of metabolism, including chronic renal failure, alcoholism, hypothyroidism, diabetes and amyloidosis.
(c) Defective immunity. Background factors include splenectomy, leukaemia, myeloma, sickle-cell disease, thalassaemia, systemic lupus and nephrotic syndrome.
Pneumococcal bacteraernia in children is non-pulmonary, and has a case fatality of 13 per cent. It is associated with otitis media, menin-gitis or an upper respiratory infection. The pneumococcus is often found in saliva. The splenectornised child is particularly prone to pneumococcal septicaemia
In the adult, pneumococcal bacteraemia has a case fatality rate of 34 per cent. It occurs particularly in elderly men with pneumonia, some of whom were splenectomised.
Improving the soil
How can we improve the resistance of the immunosuppressed against disease? There are, of course, the obvious factors such as the correction of malnutrition and ischaemia, antibiotics and, where possible, the correction of the underlying disease.
Are there any methods of inimunomanipulation of the soil? We have used transfer factor and levamisole without much benefit. Marrow and thymus transplants may help to overcome poor cellular immunity due to T cell disorders. Like-wise, impaired humoral immunity is being improved by intramuscular and intravenous inimunoglobulins and by plasmapherisis. The future holds promise with the interferons, interleukin-2, monoclonal antibodies, and the use of patching genes (by the technique of recombinant DNA) to provide vaccination against disease (Table VI).

Table VI
Methods of Immunomanipulation of T cells, B cells or Both.

T cells		
Transfer Factor		
Levamisole		
Thymosin		
Marrow)	Transplants	
Thymus)		
Interleukin 2		
Gamma – Interferon		
B cells		
Immunoglobulin		intravenous intramuscular
Plasmapheresis		
Both		
Monoclonal antibodies		
Interferons		
Patching	Recombinant DNA	Genes
Monocytes		
Thalidomide		

Splenectomy[18]
Needless splenectomy is deplorable for it may lead to fulminant infections in childhood.
Splenectomised children should have polyvalent vaccines and prophylactic penicillin for at least two

years. There is also an increased risk in adults, but this is less evident.

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