

Various Types of Specific Acquired Deficient Immune Status (SADIS) following Various Kinds of Microbial Infection - 5a. the clinical management of diseases that may produce SADIS with lymphocyte predominance

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Diseases that may produce SADIS may have lymphocyte predominance or lymphocyte depletion. There are three categories of diseases that in the advanced stage may produce SADIS (fig. 1), i.e.:

Fig. 1. Three categories of specific acquired deficient immune status (SADIS)

Category I	the Tb-type of SADIS brought about by:
	<ul style="list-style-type: none"> • Bacteria : M. tuberculosis <li style="padding-left: 20px;">: H. pylori • DNA-viruses : HBV, HPV, HSV-2, EBV • RNA-virus : HCV.
Category 2	the Lk-type of SADIS brought about by:
	<ul style="list-style-type: none"> • DNA-virus : EBV • RNA-viruses : HTLV-I, HTLV-II.
Category 3	the Lp-type of SADIS brought about by:
	<ul style="list-style-type: none"> • RNA-viruses : HTLV-III (HIV-1), HIV-2 • bacterium : M. leprae.

1) Diseases that may progress to the tuberculosis-type (Tb-type) of SADIS, comprising diseases caused by the tubercle bacillus, the Helicobacter pylori, the hepatitis B virus (HBV), the hepatitis C virus (HCV), the human papilloma virus (HPV), the herpes simplex virus type 2 (HSV-2) and the Epstein Barr virus (EBV).

2) Diseases that may produce the leukemia-type (Lk-type) of SADIS, comprising a disease caused by the EBV, and diseases caused by the human T-cell lymphotrope virus type I (HTLV-I) and the human T-cell lymphotrope virus type II (HTLV-II).

3) Diseases that may progress to the leprosy-type (Lp-type) of SADIS, comprising diseases caused by the human immunodeficiency virus type I (HIV-1), the human immunodeficiency virus type II (HIV-2) and a disease caused by the leprosy bacillus.

The Tb-type of SADIS has primary solid malignancy as

disease expression that is located in an organ of the host, e.g. the lung (bronchogenic carcinoma), the nasopharynx (nasopharynx carcinoma), the liver (primary hepatocellular carcinoma) and the cervix of the uterus (cervix carcinoma). The existence of T-lymphocyte predominance is a characteristic of the Tb-type of SADIS. In addition, there is a predominance of the cellular immune system in comparison to the humoral immune system (fig. 2).

Fig. 2. Some characteristics of the three types of SADIS

Type of SADIS	Disease expression	Lymphocytes	CMIS* HIS**
Tb-type	primary malignancy (epithelial carcinoma)	predominance	> 1
Lk-type	primary malignancy (leukemia, NHL,*** Hodgkin's dis.)	predominance	> 1
Lp-type	• AIDS, opportunistic malignancy • KK-type leprosy	depletion	< 1
		depletion	< 1

Note:

CMIS : cell mediated immune system

HIS : humoral immune system

NHL : non-Hodgkin's lymphoma

The Lk-type of SADIS has primary hematologic malignancy as disease expression that is located in tissues of organs of the host, e.g. in lymph nodes (malignant lymphoma) and in bone marrow (leukemia). Lymphocyte predominance which is based on neoplastic proliferation of lymphocytes, is a characteristic of the Lk-type of SADIS. There is also predominance of the cellular immune system when compared to the humoral immune system (fig. 2).

The Lp-type of SADIS that is brought about by HIV-1 has the acquired immunodeficiency syndrome (AIDS) as disease

manifestation. It is characterized by the emergence of opportunistic infections and the development of opportunistic malignancies as well. The Lp-type of SADIS which is caused by the leprosy bacillus has the lepromatous leprosy (LL-leprosy) as disease manifestation which is characterized by the existence of primary clinical resistance to antileprosy chemotherapy. It has neither primary nor opportunistic malignancy as disease expression. In addition, it is characterized by the absence of opportunistic infection. There is lymphocyte depletion in both diseases. Predominance of the humoral immune system in comparison to the cell mediated immune system is found in the Lp-type of SADIS (fig. 2).

The specific immune spectrum and the specific immunologic characteristics of a disease that in its Advanced stage may produce SADIS, constitute the specific immunologic fingerprint of the disease. Determination of the immunologic fingerprint of diseases following infection with the causative pathogens that can bring about the development of SADIS, may provide rational basis for the proper tackling and solving of problems that may arise in the fight against the causative organisms. Knowledge of immunologic fingerprints not only enables the diagnosis of the related disease to be made more accurately but also provides a more rational basis for effective clinical management to be based on.

Diseases of the same category of SADIS may have identical or almost identical principles of clinical management. In addition, knowledge of immunologic fingerprint has substantially broadened our knowledge and understanding of the pathways through which the disease may progress or regress. Achievement of a defined knowledge of clinical management of diseases that have undergone long-term and thorough tackling and solving of the related problems, such as tuberculosis and leprosy, may serve as rational paradigm for effective clinical management to be set up in aid of other diseases that may produce the same category of SADIS.

I) THE CLINICAL MANAGEMENT OF DISEASES THAT MAY PRODUCE THE TB-TYPE OF SADIS

Based on the characteristics of the immunologic fingerprint, the principles of the clinical management of diseases that may produce the Tb-type of SADIS are divided into the following: A) The clinical management of diseases that emerge as disease expression of the acute (L-type) and the chronic type (K-type) immune status (fig. 3).

1) The institution of "the early kill" of causative microbial pathogens through the advent of specific anti-microbial chemotherapy when disease expression is of the L-type or K-type immune status.

2) The enhancement of the "early kill" of microbial pathogens through the concomitant use of immunomodulators during the early phase of anti-microbial chemotherapy when disease expression is of the K-type immune status at start of chemotherapy.

The institution of immunotherapy with BCG following cessation of a successful anti-microbial chemotherapy for the

Fig. 3. The clinical management of diseases that may bring about development of Tb-type SADIS

Purpose: Back to basic which means back to the L-type immune status

Prevailing Immune Status		
L-type	K-type	KK-type (Tb-type SADIS)
<ul style="list-style-type: none"> early kill of microbial pathogen thru specific antimicrobial chemotherapy 	<ul style="list-style-type: none"> early kill of microbial pathogen thru specific antimicrobial chemotherapy augmentation of early kill of microbial pathogen thru immunomodulator stabilization of cure thru immunotherapy with BCG 	<ul style="list-style-type: none"> early kill of microbial pathogen thru: <ul style="list-style-type: none"> surgery chemotherapy radiotherapy stabilization of cure thru specific anti-microbial chemotherapy (when available) stabilization of cure thru immunotherapy with BCG.

stabilization of the cure when disease expression is of the K-type immune status at start of chemotherapy.

B) The clinical management of diseases that emerge as disease expression of the KK-type immune status (Tb-type of SADIS) (fig. 3).

1) The institution of the "early kill" of microbial antigen through the advent of:

1.1. surgical resection of the lesion.

1.2. cytotoxic chemotherapy.

1.3. radiotherapy,

for the regression of immune status from the KK-type to the K-type or even further to the L-type immune status.

2) The enhancement of the "early kill" of microbial pathogen through the use of specific anti-microbial chemotherapy for the stabilization of the cure following achievement of complete remission of the lesion.

3) The inoculation of BCG as immuno-therapy for the stabilization of the cure following the achievement of complete remission of the lesion when specific anti-microbial chemotherapy is not available.

A1) The institution of the "early kill" of microbial antigen through the advent of specific anti-microbial chemotherapy.

The tubercle bacillus is the prototype of microbial pathogens that can bring about the Tb-type of SADIS. The advent of adequate anti-TB chemotherapy is crucial in the fight against the tubercle bacilli before the disease may progress to disease manifestation of the Tb-type of SADIS.

Anti-TB chemotherapy has anti-microbial activity and has the added advantage of being able to induce regression of immune status from the K-type to the L-type aiming at the achievement of better protective immunity. The "early kill" of tubercle bacilli through the use of adequate anti-microbial chemotherapy is essential for the achievement of a successful result at end of treatment. Anti-tuberculosis drugs exert bactericidal activity only during a treatment period of six months⁽¹⁾.

During this period, killing of tubercle bacilli and regression of immune status take place. Prolongation of chemotherapy using the same treatment regimen produce enhancement of protective capacity without further anti-microbial activity of the drugs⁽¹⁾. Enhancement of protective immunity is based on the augmentation of bactericidal activity of the macrophage through further regression of immune status to the L-type.

The advent of anti-*Helicobacter pylori* drugs such as tetracycline hydrochloride or amoxicillin, metronidazole and colloidal bismuth subcitrate, known as the triple therapy, has been shown to be effective for the institution of the "early kill" of *Helicobacter pylori* when disease expression is of the L-type or K-type immune status. A treatment regimen consisting of colloidal bismuth subcitrate, tetracycline hydrochloride and metronidazole has been shown to eradicate *Helicobacter pylori* infection in 91% of an Australian dyspeptic population (quoted from : Asian Medical News; Medical Tribune International vol. 12, October 2, 1990).

Current anti-ulcer regimen using drugs usually termed the H₂ receptor antagonists, now designated as immunomodulators, have been successful but the ulcer recurrence is an inconvenient and sometimes a serious problem⁽²⁾. Almost 80% of duodenal ulcer patients caused by *Helicobacter pylori* that healed following the advent of H₂-receptor antagonists for the duration of 4–6 weeks, developed relapse within one year, but if an anti-microbial regimen consisting of colloidal bismuth subcitrate, metronidazole plus amoxicillin or tetracycline hydrochloride (triple therapy) is used as well to control *Helicobacter pylori*, the relapse rate is reduced to less than 10% if it is completely eradicated^(3,4,5). Two weeks treatment using triple therapy is adequate to achieve eradication of *Helicobacter pylori* in most patients⁽²⁾.

The result of treatment using interferon and aciclovir in patients suffering from chronic hepatitis B, revealed that both drugs are effective for the institution of the "early kill" of HBV, when disease expression is of the K-type immune status. The result of anti-viral treatment in 12 patients suffering from chronic hepatitis B conducted in 1985 revealed that combination therapy of interferon and aciclovir appeared to be obviously more effective than when interferon or aciclovir was given as monotherapy⁽⁶⁾. Alpha-interferon has a favourable effect on viral replication and on the levels of liver enzymes in 25–50% of selected patients with chronic hepatitis B virus infection^(7,8). Active viral replication of HBV is characterized by the persistent presence of HBs-Ag, HBe-Ag and HBV-DNA-polymerase in blood.

The presence of HBs-Ag only indicates the emergence of virus-latency; anti-HBe-antibody may also be encountered. During the latent phase of virus elimination, HBs-Ag is no longer detectable in blood; anti-HBs-antibody and anti-HBe-antibody may be encountered⁽⁹⁾. Anti-viral treatment in chronic hepatitis B patients is exclusively meaningful when active viral replication exists which can be confirmed by a positive result of HBs-Ag and HBe-Ag test⁽⁹⁾. Combination of interferon plus aciclovir may induce a state of virus-latency in 80% of chronic HBe-Ag

positive patients⁽⁶⁾; some may even be cuffed⁽¹⁰⁾. The accelerated seroconversion of HBe-Ag coincides with the improvement of clinical, biochemical and histological parameters⁽¹⁰⁾.

Based on the result of a study on the efficacy of interferon given to 18 patients suffering from clinically apparent cirrhosis of the liver related to chronic hepatitis B, Hoofnagle et al.⁽¹¹⁾ pointed out that it is quite reasonable to treat patients with cirrhosis of the liver due to chronic hepatitis B with alpha-interferon. During treatment for the duration of average 12 weeks, HBe-Ag and hepatitis B-virus-DNA disappeared from blood in 12 patients. One to 14 months following cessation of treatment, hepatitis B-virus-DNA was encountered again in 6 of them. The other 6 patients in whom hepatitis B-virus-DNA was no longer found, remission was achieved in all of them. During a follow-up period of 4.2 years, no signs of cirrhosis were encountered⁽¹¹⁾.

At present, there are no uniformly effective drugs against infection with HCV, an RNA-virus. Clinical drug trials have shown that treatment using recombinant interferon-alpha for six months can normalize liver function in up to 46% of patients. However, the relapse rate following cessation of successful therapy is high (up to 51%)⁽¹²⁾.

Treatment with interferon-alpha has a favourable effect on serum liver enzyme activities and on the histologic abnormalities in approximately 50% of patients with chronic hepatitis C^(13,14). There is correlation of the response to treatment and the decrease of the number of hepatitis C-RNA in serum⁽¹⁵⁾. Alpha-interferon and beta-interferon, derived respectively from leukocyte and from fibroblast, are produced in the body of the host as natural response to viral infection. They have a very broad spectrum of anti-viral activity⁽¹⁶⁾. Gamma-interferon is produced by T-lymphocyte following antigen specific and non-specific activation and is a lymphokine or cytokine with immunomodulating capacity⁽¹⁷⁾.

Anti-viral chemotherapy must have the capacity to stop replication of virus, termed the virustatic action, in infected cells without bringing about the development of radical alteration in the normal metabolism of cell. A virologic aspect that deserves attention is that available drugs are in general effective against viruses which are replicating and not effective against viruses which are not replicating in the cell of the host, the latter being encountered in latent herpes virus infection⁽¹⁶⁾.

An initial episode of herpes genitalis is a good indication for anti-microbial treatment with aciclovir⁽¹⁶⁾. Aciclovir has a selective virustatic action. This action is based on the inhibition of the viral DNA-polymerase which is essential for the replication of the viral DNA. The herpes simplex virus type 1 (HSV-1) and the herpes simplex virus type 2 (HSV-2) are sensitive and the varicella zoster virus (VZV) is moderately sensitive to aciclovir in vitro⁽¹⁰⁾. There is some activity of aciclovir against the EBV⁽¹⁶⁾. The cytomegalovirus (CMV) is insensitive to aciclovir^(10,16).

Aciclovir is not effective against latent herpes virus infection^(10,16) and has only a marginal therapeutic effect on recurrent herpes infection of the skin and mucoid membrane, provided it is employed in the early phase of the disease⁽¹⁰⁾. The most striking

characteristic of herpes viruses is that they persist in the body of the host following infection⁽¹⁰⁾. Aciclovir shortens the duration of viral shedding, the time for the achievement of cure, the duration of symptoms, and inhibits the development of new lesions during treatment of patients suffering from herpes genitalis⁽¹⁶⁾.

Treatment using aciclovir doesn't have influence on the rate of development and the severity of herpes genitalis relapses. Foscarnet (phosphonoformate) inhibits the DNA-polymerase of herpes virus⁽¹⁸⁾. It is mainly used in immunocompromised patients with resistant HSV and VZV infections to aciclovir and with resistant CMV infection to ganciclovir⁽¹⁶⁾. An synergistic anti-CMV-effect in vitro of ganciclovir and foscarnet has been reported^(19,20). Casuistic reports and observations revealed encouraging results of treatment with the above combination^(21,22).

A2) The enhancement of the early kill of microbial pathogen through the advent of immuno-modulators.

The "early kill" of microbial pathogens through the use of adequate anti-microbial chemotherapy can be augmented by the use of immuno-modulators, such as cimetidine, isoprinosine and levamisole. The advent of cimetidine concomitantly during the early phase of anti-TB chemotherapy accelerate the incidence of sputum negativity⁽²³⁾. Immuno-modulators enhance the microbicidal activity of the macrophage. When given in the absence of anti-microbial chemotherapy, immuno-modulators may delay the progression of immune status from the K-type to the KK-type (SADIS). It is intriguing to speculate that immuno-modulators have the capacity of an immuno-biological response modifier. They likely have the capacity to modify immune status from the prevailing one to a previous one from which it has progressed or regressed. Immuno-modulator as a therapeutic adjunct in the administration of anti-microbial chemotherapy has to be given during the early phase of chemotherapy or even preceding the commencement of chemotherapy. When given following cessation of a successful anti-microbial chemotherapy, immuno-modulator may have a deleterious effect on the outcome of chemotherapy; it may accelerate the development of relapse following cessation of successful chemotherapy.

It can be expected that the concomitant use of immuno-modulator and specific anti-microbial chemotherapy in patients suffering from diseases that can produce the Tb-type of SADIS in their chronic stage (K-type immune status), may accelerate the regression of immune status from the K-type to the L-type. This implies that in patients with gastric ulceration due to *Helicobacter pylori* infection, healing of ulcer will be accelerated.

The use of immuno-modulator in patients with chronic hepatitis can be expected to delay the progression of chronic hepatitis to the development of malignancy.

A3) The stabilization of cure through the advent of immuno-therapy.

Inoculation of BCG for the purpose of immunotherapy following cessation of a successful anti-tuberculosis chemotherapy in patients with chronic tuberculosis, gives rise to further regression of immune status from the K-type to the L-type, resulting in the generation of better protective immunity for

better stabilization of the cure achieved at end of chemotherapy⁽²⁴⁾.

Inoculation of BCG as immunotherapy has to be carried out following cessation of a successful anti-TB chemotherapy. When given preceding the commencement of chemotherapy, inoculation of BCG may have a deleterious effect on the prevailing immune status as was evidenced by the development of a down-grading reaction in the immune spectrum of tuberculosis, resulting in a further deterioration of protective immunity⁽²⁵⁾. When given during the implement of anti-TB chemotherapy, BCG will be killed by the anti-microbial activity of the anti-TB drugs.

The result of specific immunotherapy with BCG for the enhancement of protective immunity achieved at end of a successful anti-TB chemotherapy, opens new prospects for the investigation whether inoculation of BCG as non-specific immunotherapy can enhance protective immunity achieved at end of a successful anti-microbial chemotherapy in patients with chronic disease due to for instance *theHelicobacterpylori* or the hepatitis B virus infection.

B1) The institution of the "early kill" of microbial pathogen through the mechanism of regression of the KK-type immune status.

The existence of an optimally functioning immune defense system is a *conditio sine qua non* for the proper functioning of anti-microbial activity of anti-tuberculosis drugs.

Progression of the K-type immune status which has chronic TB as disease expression to the KK-type immune status which has primary localized malignancy as disease manifestation, is characterized by the existence of a defective immune defense system especially related to cell mediated immunity.

Anti-TB chemotherapy is no longer effective when employed to tuberculosis patients during the advanced stage of the disease that have primary malignancy as disease expression. (unpublished data). It is like doing shadow boxing; much energy is spent without ever hitting the opponent.

Based on its localized character, clinical management of primary malignancy as disease manifestation of the TB-type of SADIS, whatsoever is the causative pathogen, should aim at the achievement of rapid complete remission of the lesion, i.e. through the implement of surgical resection of the malignancy as far as it is still operable, curable and resectable. The principal advantage of surgery over radiotherapy or cytotoxic chemotherapy lies in the absence of the development of secondary malignancy. Lymphocyte predominance is a characteristic of the Tb-type of SADIS. Clinical management of primary malignancy as disease expression of the TB-type of SADIS, no matter what the causative organism may be, should aim at the achievement of a complete remission of the malignancy through normalization of the prevailing lymphocyte predominance by way of the advent of immuno-suppressive medication especially when the disease is no longer resectable or operable. Immuno-suppression through the advent of radiotherapy and/or the use of cytotoxic chemotherapy are eligible tools for the normalization of the lymphocyte predominance.

Radiotherapy remains a localized form of treatment for what

is usually a disease that tends to disseminate. Its principal advantage over surgery is the preservation of structure and function of treated organs⁽²⁶⁾. It is unlikely that a malignancy with a mass greater than 5 cm in diameter can be sterilized by radiotherapy⁽²⁷⁾. Radiation induces profound lymphopenia in lymphoid organs and in the general circulation as well. In addition, it suppresses most immuno-competent cell function⁽²⁸⁾. X-ray irradiation has a toxic effect on proliferating and intermitotic cells as well and has the effect of cycle-nonspecific drugs in addition. The great majority of immunologically competent lymphocytes are in the intermitotic phase of the proliferating cycle. Consequently, radiotherapy may reduce the number of blood or tissue lymphocytes and may cause a generalized depletion of immunologically competent cells⁽²⁸⁾.

Cytotoxic chemotherapy is not selectively toxic for competent lymphocytes but is potentially capable of killing any cell that has the capacity to replicate⁽²⁸⁾. Based on their capacity to kill cells in different phases of the mitotic cycle, cytotoxic drugs can act as phase-nonspecific drugs, cycle-specific drugs and cycle-nonspecific drugs. As cycle-nonspecific drugs, cytotoxic drugs are equally toxic to both proliferating and intermitotic cells⁽²⁸⁾. Consequently, reduction of the number of lymphocytes or even lymphocyte depletion may be the outcome of therapy as a great deal of the immuno-competent lymphocytes are in an intermitotic phase of the proliferating cycle. In general, cytotoxic chemotherapy and radiotherapy are given separately and in sequence⁽²⁹⁾.

Corticosteroids are important adjuncts to the advent of immuno-suppressive therapy using cytotoxic chemotherapy and/or radiotherapy. The production of cytotoxic T-lymphocytes from the non-cytotoxic precursor cells is diminished by corticosteroids in vitro and in vivo as well^m. Corticosteroids appear to stop the T-helper cells from secreting T-cell growth factor by an indirect effect. They actively preclude macrophages from secreting interleukin-1 which is known to interact with the T-helper cells that subsequently elaborate T-cell growth factor⁽³⁰⁾. Consequently, based on their effect on cell mediated immunity, corticosteroids reduce the number of lymphocytes. The effect of corticosteroids on humoral immunity is less profound. Chronic administration of the drug decreases IgG synthesis, while short-course treatment doesn't dampen primary or secondary antibody responses⁽³⁰⁾.

The achievement of complete response to radiotherapy and/or cytotoxic chemotherapy as is based on the achievement of complete remission of the disease is a good prognostic sign. Achievement of complete remission of pathologic lesion following surgical resection or following immuno-suppressive medication through the advent of radiotherapy and/or cytotoxic chemotherapy means the achievement of cure which implies the achievement of immune status inherent in healthy naturally infected individuals or in healthy BCG-vaccinated individuals in the immune spectrum of tuberculosis.

B2) The enhancement of the early kill of microbial pathogen through the use of anti-microbial chemotherapy.

The institution of specific anti-microbial chemotherapy when available following the achievement of complete remission of malignancy through the advent of surgery, cytotoxic chemotherapy and/or radiotherapy, is essential for the stabilization of cure, the mechanism of which is based on the eradication of the remaining causative microbial pathogens.

Beside its killing effect on the remaining causative microbial pathogens, anti-microbial chemotherapy has the added advantage of being able to bring about a further shift of the position of immune status in the immune spectrum of the disease from that of healthy subjects following natural infection to that of subjects following vaccination.

B3) Stabilization of the cure following complete remission of malignant lesion through the advent of immuno-therapy.

When specific anti-microbial chemotherapy is not available or when the causative pathogen is not known, inoculation of BCG as immuno-therapy is the eligible alternative measure for the stabilization of cure. Immuno-therapy through the advent of BCG is aimed at bringing about further shift of the immune status that has taken place from the KK-type to the K-type following complete remission of malignant lesions through the advent of surgery, radiotherapy or cytotoxic chemotherapy. In other words, immuno-therapy with BCG following complete remission of malignant lesions through the advent of surgery, radiotherapy and/or cytotoxic chemotherapy, may bring about a further shift of the position of immune status in the immune spectrum of the disease from that of healthy individuals following natural infection to that of healthy individuals following vaccination.

In cancer therapy, immuno-therapy is usually employed after chemotherapy and radiotherapy. Non-specific systemic immuno-stimulation can be carried out using agents such as BCG, with the aim of general stimulation of immunologic responsiveness.

Bacillus Calmette Guerin (BCG) is a viable attenuated strain of *M. bovis* obtained by progressive reduction of virulence via culture medium enriched with beef bile). It is a whole bacillus vaccine. Bacillus Calmette Guerin acts mainly by stimulating the reticulo-endothelial system, i.e. the activation of T-cell and lymphokine production and the activation of macrophage. It also stimulates natural killer cells which can kill different malignant cells non-specifically and without previous sensitization⁽³¹⁾. It is possible that macrophages activated by BCG are more active killer cells and are more efficient in cleaning antigens or antigen-antibody complexes, or are capable of inducing active participation of other cells of the immune system in the fight against proliferating tumor cells⁽³¹⁾. Bacillus Calmette Guerin appears to enhance the production of stem cells, as was measured by hematopoietic colony formation. In addition, some investigators have made the suggestion that BCG cross-reacts immunologically with hepatoma, melanoma and leukemic cells. Immuno-therapy with BCG is employed as adjuvant treatment following cytoreductive treatment of measurable cancer in order to destroy micrometastasis and the residual tumor cells⁽³¹⁾.

II. THE CLINICAL MANAGEMENT OF DISEASES THAT MAY PRODUCE THE LK-TYPE OF SADIS. (FIG. 4).

Fig. 4. The clinical management of diseases that may bring about development of Lk-type SADIS

Purpose: Back to basic which means back to L-type immune status

Prevailing Immune Status		
L-type	K-type	KK-type (Lk-type SADIS)
<ul style="list-style-type: none"> • Early kill of microbial pathogen thru specific antimicrobial chemotherapy 	<ul style="list-style-type: none"> • Early kill of microbial pathogen thru specific antimicrobial chemotherapy • Augmentation of early kill of microbial pathogen thru immunomodulator • Stabilization of cure thru immunotherapy with BCG. 	<ul style="list-style-type: none"> • Early kill of microbial pathogen thru: <ul style="list-style-type: none"> • chemotherapy • radiotherapy • Stabilization of cure thru specific anti-microbial chemotherapy (when available) • Stabilization of cure thru immunotherapy with BCG.

Like in patients with the Tb-type of SADIS, there is T-lymphocyte predominance in patients with the Lk-type of SADIS. There is also predominance of the cellular immune system when compared to the humoral immune system (fig. 2).

Based on the characteristics of the immunologic fingerprint and its resemblance to the Tb-type of SADIS, the principles of clinical management of diseases that may produce the Lk-type of SADIS are the following:

A) The clinical management of diseases that emerge as disease manifestation of the acute (L-type) and chronic (K-type) immune status.

1) The institution of the "early kill" of causative microbial pathogens through the advent of specific anti-microbial chemotherapy when disease expression is of the L-type or the K-type immune status.

2) The augmentation of the "early kill" of causative microbial pathogens through the advent of immuno-modulators during the early phase of anti-microbial chemotherapy when disease expression is of the K-type immune status at start of chemotherapy.

3) The institution of immuno-therapy following cessation of a successful anti-microbial chemotherapy for the stabilization of the cure when disease expression is of the K-type immune status at start of chemotherapy.

B) The clinical management of diseases that emerge as disease expression of the KK-type immune status (Lk-type of SADIS).

1) The institution of the "early kill" of causative microbial pathogens through the advent of:

1.1. cytotoxic chemotherapy

1.2. radiotherapy

for the regression of immune status from the KK-type to the K-type or even further to the L-type immune status.

2) The enhancement of the "early kill" of causative microbial pathogens through the use of specific anti-microbial chemo-

therapy for the stabilization of the cure following achievement of complete remission of the disease.

3) The inoculation of BCG as immuno-therapy for the stabilization of the cure following achievement of complete remission of the disease when specific anti-microbial chemotherapy is not (yet) available.

A. The clinical management of diseases that emerge as disease manifestation of the acute (L-type) and the chronic (K-type) immune status (fig. 4).

Achievement of cure following EBV-infection occurs spontaneously in general in the course of 4–6 weeks. In some of the patients symptoms may persist during months or years; these patients are considered as suffering from chronic persistent EBV-infection. Most striking is the presence of antibodies against EBV-early antigen (EBV-EA) often in high titers⁽³²⁾. There is hitherto still no effective drug available for the "early kill" of EBV during the acute and the chronic stage of the disease. According to Lange and Van der Noorda^m, aciclovir has some activity against EBV.

Of the herpes viruses, the herpes simplex virus type 1 (HSV-1) and the herpes simplex virus type 2 (HSV-2) are sensitive to concentrations of aciclovir; the Epstein Barr virus and the cytomegalovirus (CMV) are not sensitive to aciclovir. The Varicella-Zoster-virus (VZV) is moderately sensitive to aciclovir⁽¹¹⁾. Aciclovir is a selective virustaticum. The drug is active following conversion into aciclovir-triphosphate which takes place in the cell that is infected with the virus. Aciclovir is much easier bound to viral thymidine-kinase than to thymidine-kinase of the host. The action of aciclovir-triphosphate is based on inhibition of the viral DNA-polymerase which is essential for the viral DNA replication. It is important to note that aciclovir is not effective in latent viral infection⁽¹⁰⁾.

No effective drugs are hitherto available for the "early kill" of HTLV-I and HTLV-II during the acute and chronic stage of the disease. In a small group of Japanese patients suffering from HTLV-I infection in the chronic stage of the disease (tropical spastic paraparesis), improvement has been observed following treatment with corticosteroids⁽³²⁾. In other group of patients, this favourable response of treatment was not confirmed^(3,4).

The result of analysis on the significance of the mobility of the spectrum of the pattern of tuberculin reaction in the immune spectrum of tuberculosis related to the use of immuno-modulator⁽²³⁾, opens new prospects for the investigation whether immuno-modulators given to subjects with chronic disease caused by **EBV**, HTLV-I or HTLV-II can accelerate the achievement of spontaneous cure or delay the progression of the immune status of chronic disease (K-type) to the Lk-type of SADIS.

On the basis of the result of the advent of immuno-therapy with BCG in tuberculosis patients following the achievement of successful result of chemotherapy⁽²⁴⁾, it is intriguing to speculate that immuno-therapy with BCG given to subjects with chronic disease caused by EBV, HTLV-I or HTLV-II following the achievement of successful result of chemotherapy using effective drugs that hopefully will be made available, may stabilize the achievement of cure.

B. The clinical management of diseases that emerge as disease expression of the KK-type immune status (Lk-type of SADIS) (fig. 4).

Unlike in patients with the Tb-type of SADIS, in patients with the Lk-type of SADIS, primary malignancy as disease manifestation of SADIS is located in tissues of various organs of the host and tends to have a disseminated rather than a localized character. Surgical resection of the disease is in general not indicated as an effort to achieve complete remission of the lesion. In patients with the adult T-cell leukemia as disease expression of the Lk-type of SADIS due to HTLV-I, the result of treatment with cytostatica is in general bad; remission is not observed or only of short duration (quoted from: S. Daenan; *Nederl. Tijdschr. v. Geneesk.* 1984, 128, 957-960). Aggressive treatment is considered necessary, but the "classical" combination regimens have very little influence on the survival. Usually there is only a response of short duration. Deoxycoformycine (DCF) has been given to a patient with the adult T-cell leukemia with good result. Complete remission was observed.

Other cytostatics for further eradication of the abnormal T-cell (a combination of high dosage corticosteroids, cytarabine, vincristine, doxorubicine and cyclophosphamide) were administered following the achievement of complete remission in an effort to "consolidate" this effect. A bone marrow aplasia developed following the use of the above combination treatment. There was no development of relapse during a follow-up period of 12 months and the patient remained in good health without specific treatment (quoted from: S. Daenan, *Nederl. Tijdschr. v. Geneesk.* 1984, 128, 957-960).

Treatment with interferon can be considered on the basis of the probable viral genesis⁽³⁵⁾. Deoxycoformycine (DCF) inhibits specifically the adenosinedeaminase which leads to cumulation of deoxyadenosine and deoxyadenosine triphosphate that are toxic for the cell. A peculiar effect of the drug is that only lymphocytes, in particular T-lymphocytes, are sensitive to DCF (quoted from: S. Daenan; *Nederl. Tijdschr. v. Geneesk.* 1984, 128, 957-960).

Patients suffering from the hairy cell leukemia with splenomegaly and pancytopenia should be treated by splenectomy. Chemotherapy should be reserved for those patients that fail to respond to splenectomy or that exhibit development of relapse after a transient response to splenectomy⁽³⁶⁾.

The non-Hodgkin's lymphomas are a heterogenous group of malignancies which primarily involve lymphoid tissues. Radiotherapy and/or chemotherapy are useful tools of management in patients with NHL. A suitable lymph node, which emerges as a single palpable lymph node, should be identified and the whole node removed at operation with the minimum of trauma⁽³⁷⁾. In cases with single site involvement of bowel, i.e. at the ileocaecal junction or the stomach, resection with bowel anastomosis is indicated⁽³⁷⁾. Histopathologic diagnosis is of essential importance for the choice of treatment and the prognosis of patients with NHL. New diagnostic and therapeutic developments in the last decades have shown that more patients with NHL can be cured⁽³⁸⁾. Beside histopathologic examination, immuno-pheno-

typifying has also to be done in order to know whether the NHL is of the B- or the T-cell origine⁽³⁹⁾.

Patients in stage I or II are treated with radiotherapy on the affected lymph node station or on the affected lymph node stations (the so-called involved field radiation therapy^(39,40). The disease-free 5-10 year survival is 60% and 50% respectively⁽⁴¹⁾. This latter group of patients are likely cured⁽³⁹⁾. The involved field radiotherapy is hitherto the only curative treatment modality in patients with low grade non-Hodgkin's lymphoma in stage I or II⁽³⁹⁾. Young age-group (< 40-60 year) and/or small tumor mass are thereby the most important favourable prognostic factors. More extensive radiotherapy, i.e. on more lymph node stations, or combination therapy with chemotherapy, has not led to an obvious improvement of the chance for the achievement of cure⁽³⁹⁾.

In patients with stage III and IV NHL, the follicular lymphoma is very sensitive to chemotherapy^(39,40). In 50-60% of patients, complete remission is achieved and in 10-30% a good partial remission is achieved with cytostatics like chlorambucil, cyclophosphamide, or a combination therapy with cyclophosphamide, vincristine and prednison (CVP). The advantage of the combination treatment is that remission is achieved earlier in the course of treatment^m. The median duration of remission is 2-3 years and afterwards treatment of relapse cases with the so-called second line chemotherapy leads to remission of 2-3 years duration in 60-70% of the patients⁽⁴²⁾. The mean duration of survival in patients with low grade NHL in stage III or IV is 7 years.

Although the results of some investigations reveal a higher remission-percentage and prolongation of disease-free interval, the total survival duration with more intensive chemotherapy does not appear to be prolonged⁽⁴³⁾. Of much influence on the prognosis is whether or not histologic transformation to a higher degree of malignancy has taken place. In the course of the disease this transformation occurs in 30-40% of the patients. The prognosis hereafter is bad. Despite aggressive chemotherapy, the median duration of survival is only 1 year⁽³⁹⁾. Long term treatment with interferon-alpha appears to lead to remission in 40% of patients with follicular lymphoma^{@3>}

At the moment examinations are done in several clinical investigations to know whether addition of interferon-alpha to conventional chemotherapy leads to improvement of the result of treatment⁽³⁹⁾. Chemotherapy is given to almost every patient suffering from NHL located in the pancreas. Complete remission during a minimal follow-up period of 18 months was observed in 50% of patients under treatment with chemotherapy as was reported by de Jong et al.⁽⁴⁴⁾.

Treatment of NHL of intermediate and high grade malignancy consists primarily of combination chemotherapy. In some treatment schedule, radiotherapy is added as consolidation treatment, but its additive value has still to be confirmed in an at random investigation^(45,46). Patients with localized intermediate grade lymphoma may be put under treatment with radiotherapy alone, but apart from the large cell lymphomas, the risk of relapse is high⁽³⁷⁾.

Patients with stage II–IV large cell lymphoma are at present treated intensively with combination chemotherapy. Complete remission rate as high as 80% or more have been reported and as many as 40% of patients are cured⁽³⁷⁾. Patients with stage I (10–20% of all patients with an intermediate or high grade NHL) can for the greater part (80–90%) be cured with a limited number of CHOP-courses (cyclophosphamide, doxorubicine, vincristine, prednison) followed by involved field radiotherapy^(45,46).

In stage II–N, a remission percentage of 40–60% is observed with the standard treatment CJOP. With this treatment, 30% of all patients may be cured⁽⁴⁷⁾.

Hodgkin's disease (HD) is a multifocal disease⁽⁴⁸⁾. The disease begins in a single lymph node followed by dissemination to adjacent lymph nodes and then to other organs in a fairly consistent pattern⁽⁴⁹⁾. There are the lymphocyte predominance and the lymphocyte depletion type in HD. Lymphocyte predominance type is observed in younger patients, is usually limited in extent and has an excellent prognosis. Most investigators feel that the lymphocyte-infiltrate found in HD lesion represents the cellular immune response against the tumor and correlates with a more favourable prognosis.

Lymphocyte depletion type is at the opposite end of the spectrum, usually presenting with wide-spread disease and constitutional symptoms and having a poor prognosis⁽⁵⁰⁾. Depletion of lymphocyte is comparatively rare in HD^(51,52). Progression from lymphocyte predominance to lymphocyte depletion is associated with worse prognosis⁽⁵³⁾. The prognosis of patients suffering from HD is markedly better than that of patients suffering from NHL as was based on survival chances⁽⁵⁴⁾.

There is no standard treatment in patients with HD⁽⁵⁵⁾. Radiotherapy is used in patients with HD; chemotherapy is at least a component of treatment for advanced disease⁽⁵²⁾. Since the advent of radiotherapy and chemotherapy for treatment of patients suffering from HD, the prognosis is impressively improved; 70% of the patients under treatment may even make recovery⁽⁵¹⁾.

Both chemotherapy and radiotherapy eradicate the disease under certain circumstances. At present time, the best approach to treatment is to use either radiotherapy or combination chemotherapy alone in the appropriate stage⁽⁴⁸⁾. Radiotherapy and chemotherapy are also recommended for treatment of HD⁽⁵⁶⁾. For most patients with early HD (stages I-IIA), radiotherapy to a mantle field remains the treatment of choice. Approximately 70% of patients will be cured using radiotherapy alone. Patients in whom relapse develops are put under treatment with chemotherapy⁽⁵²⁾.

It is unlikely that a tumor with a mass greater than five centimeter in diameter can be sterilized and the dose of radiation would have to be very high⁽⁵⁷⁾. Patients with bulky mediastinal lymph node enlargement are usually treated with chemotherapy initially as are patients with advanced HD, many older patients and those with B symptoms or unfavourable histology⁽⁵²⁾. Approximately 30% of patients have B symptoms as defined by the Ann Arbor staging classification. B-symptoms include night sweat, unexplained weight loss of more than 10% in 6 months

before diagnosis and fever of more than 38°C with no obvious infection⁽⁵²⁾.

Patients with advanced HD (stages IIB-IVB) should be put under treatment with chemotherapy. Evidence reported by a number of clinical trials now suggests, that adriamycin containing combinations should have a role in the primary treatment of advanced HD. Adriamycin, bleomycin, vinblastine and dacarbazine (ABVD) have been used alone or in combination with MOPP (mustine, vincristine, procarbazine, prednisolon) by a number of centers, and existing data suggest that this may be associated with improved cure rates⁽⁵²⁾.

On account of the prolonged survival in patients that have been put under treatment, late adverse reaction due chemotherapy may emerge, especially the development of neoplasia, in particular the hematologic malignancies⁽⁵¹⁾.

Since the application of the megavolt apparatus and later the polychemotherapy it is possible to obtain spectacular response percentages, resulting in 80–90% disease-free interval in the early stages^(58,59) and 60–70% in the advanced stages of the disease⁽⁶⁰⁾. A child with HD should be treated primarily with chemotherapy⁽⁶¹⁾.

Radiotherapy in children has important disadvantages. Radiotherapy in the period of growth and development appears to be able to bring about growth disturbances of the tissue under treatment which results in misformation. Besides, secondary tumor may develop following radiotherapy.

In a study on the efficacy of cytostatic therapy alone without additional radiotherapy in children with HD of all stages, Behrendt⁽⁶¹⁾ has given to children with small (less than 4 cm) lymph node tumors cytostatic therapy according to MOPP scheme. Children with initially big (more than 4 cm) lymph node tumors have been given the same cytostatic therapy plus involved field radiotherapy as complementary therapy. The result of the study revealed that of the 16 children treated with chemotherapy alone, survival was 100% during follow-up periods ranging from 27 to 123 months (median 74 months). Recurrence-free survival in this group of children amounted to 87.5%. The survival of the 14 children given additional radiotherapy amounted to 93% during follow-up periods ranging from 26 to 92 months (median 58 months). Recurrence-free survival in this group of children amounted to 85%. Behrendt⁽⁶¹⁾ made the conclusion that a child with HD should be treated primarily with chemotherapy.

The achievement of complete remission of disease manifestations of the Lk-type of SADIS means the achievement of cure and the regression of immune status from the KK-type to the K-type or even to the L-type, resulting in the augmentation of the microbicidal activity of the macrophage. Like in the Tb-type of SADIS, it can be expected that in the Lk-type of SADIS specific chemotherapy against the causative organism (when available) may be given following the achievement of complete remission of the disease with chemotherapy and/or radiotherapy in order to stabilize the cure. When specific chemotherapy against the causative organism is not available, inoculation of BCG as immuno-therapy may then be contemplated.

Bacillus Calmette Guerin was first tried by Mathd and

coworkers in patients that suffer from acute lymphocytic leukemia. The attempt was based on the experimental observation that drugs were not able to kill all the tumor cells and that other means, such as immuno-therapy, were therefore considered necessary to kill the residual leukemic cells⁽³¹⁾. Bacillus Calmette Guerin was found to be effective in leukemic mice if the number of residual malignant cells did not exceed 10^5 ⁽³¹⁾. The rationale behind the above finding must be based not on the direct killing effect of BCG but on the effect of BCG on the bactericidal effect of the macrophage. Patients receiving weekly doses of BCG by scarification for a total duration of 5 years following complete remission of acute lymphocytic leukemia through the advent of chemotherapy and radiotherapy (of the central nervous system) appear to have responded best since 7 of 20 (35%) are still in remission 19 years after initiation of treatment. In contrast, only 21 of 269 children (17.8%) receiving maintenance chemotherapy alone survive for more than five years⁽³¹⁾.

Immuno-therapy with intradermal BCG (approximately 10^6 viable bacilli) following radiotherapy in patients with lymphoma (stage IA and stage IIA) give rise to a lower incidence of relapses and longer duration of remission⁽³¹⁾.

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