

A Constitution Dependent QOL Assessment

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Abstract

According to the reports from Ministry of Health in each country, the average life spans were expanded over the past century. This trend is expected to be extended further in the future and at the same time continuous efforts should be made. That indicates that the quantitative objective, as one of the objectives people have aimed at since ancient times to attain the perpetual youth and longevity, are almost achieved in this way. However, as the next objective, it is necessary for us to be concerned about improving the more advanced quality of life.

In an effort of improving the quality of life, other than the western medicine, we have attempted to bring many traditional medical practices, including the Oriental medicine, from various parts of the world into the medical field as alternative medicine. Judging both positive and negative aspects by the evaluation standard of the Western medicine, we try to obtain numerical values of QOL, and after that, set a numerical target for improvement of QOL. Some methods of alternative medicine taken in this review are acupuncture moxibustion, Chinese medicine and other traditional medicine. Above all, WHO suggests selecting the suzerain nation of acupuncture moxibustion, which has been developed in the Oriental countries and realized as a specialized cure, by raising good & bad points and ascertaining which nation advocating the best modeling method could be. At the moment for evaluating CAM, for example, what kind of methods is/are suitable for evaluating each CAM. We have been trying to propose the peripheral leukocyte is one of the best ways for evaluating CAM. Our trials are hot spring hydro therapy, acupuncture and moxibustion, light exercise and undie heating. In these evaluations, we found the common results from leukocyte effects which exhibited strong correlation for the regulation. The contents are the result from the data showing the much in number tend to downly regulate, on the other hand lower number one is up-regulated. This kind of regulation showed within a 24 hrs, for the leukocyte subsets, granulocyte and lymphocyte are changed under circadian rhythm. So for purpose of evaluating leukocyte deviation, we set the point for evaluation at the same-time zone from the first set of evaluation. Under these condition, we got a same results reproductively that the whole number of leukocyte, and its subset, granulocyte and lymphocyte also regulated within a 24 hrs. This kind of phenomenon is the case that we confirm a lot of kind of CAM and repetition. However, the life span of leukocyte are at least 3-4 days and no such a drastic apoptosis was induced such a stimulation. For the purpose of scientific explanation, we proposed that the emotional hormone are concern this change of leukocytes population. For the results of this hypothesis, there were reasonable change were seen in the peripheral blood about emotional hormone, adrenaline and dopamine. Other hormone concern thyroid grand was not changed significantly. In this review, I plan to collect evidence and judge them with the content suggested in the case of CAM setup. In other words, as a judging standard, setting immunologic factors as main items, we will judge superior and inferior of methods of each country. Recommending not only quantitatively, but also qualitatively to evaluate "balance of the lymphocyte which is the associate of the white blood corpuscle and the polymorph" as a standard of the alternative medicine in the concept of this international medical magazine.

Keywords: QOL; Constitution; Emotional hormone; Leukocyte subset; Immunological factors

Abbreviations: CAM: Complementary and Alternative Medicine; CD: Cluster of Differentiation; DM: Diabetes Mellitus; FCM: Flow Cytometry; MHC: Major Histocompatibility Antigen; QOL: Quality of Life; VAS: Visual Analog Scale

Introduction

The urgent need for QOL assessment

The recent excessive commercialization is particularly confusing for patients and doctors who seek remedies for heretofore undefined symptoms. Furthermore, since these treatments have not undergone strict testing, they are not always safe and the same drug may have different effects according to the individual patient and dosage. Complicated considerations are necessary for the application of practices such as those found in Chinese traditional medicine. Recently, alternative and complementary medicines together with oriental and traditional medicines have attracted much attention. This new interest includes aromatherapy and herbal medications, acupuncture, moxibustion and yoga. However, these therapies have not been well defined. Some are simply based on legend or belief while others are traditionally applied but without scientific evidence. Then the

assessment of each therapy and remedy need for their capacity through a scientific methods especially developed by Western Medicine. Although the word Alternative and Complementary Medicine is not popular enough in Japan than US and European countries, because in oriental countries so called Alternative and Complementary Medicine in Europe and north America is authorized medicine but not alternative one in the long histories in the world. Here I would like to introduce you where the alternative and complementary medicine now in Japan as well as in each country in the world and where should it be going in the future.

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The best scale for QOL assessment to the medicine in the East and the West

The Alternative and Complementary Medicine Society defines alternative and complementary medicine “the modern Western medicine which has not been verified scientifically and practiced at the daily clinic.” In the U.S., it is called the alternative medicine or the Complementary and Alternative Medicine (CAM). Anyway it is the medicine that is not lectured at the medical school and practiced at the daily clinic. The medicine can be classified into either the conventional medicine or the unconventional medicine. The conventional medicine is also called the modern Western medicine, scientific medicine or technical medicine, and the unconventional medicine is called the alternative, complementary, natural or fringe medicine. In Japan, the alternative medicine contains the traditional Chinese medicine, acupuncture and judo reduction etc. established as the Eastern medicine and they have their own independent long history. Since the herbal medicine is not insured in Japan, some insist it is not belong to the alternative medicine. However it is considered as alternative medicine in the West. Thus the position of the alternative medicine is various, so it might be recognized uniformly. There are many kinds of medicine including Ayurvedic Medicine in the world; therefore it is not many who can receive benefit from the Western medicine like us in Japan. The World Health Organization classifies 65-85% of the world health control business into the “traditional medicine”. In other words, if these traditional medicines are practiced in the West, it is classified into the alternative medicine. The medicine practiced in today’s Japan is called the Japanese medicine, and it is thought as one of the Far Eastern medicine like Chinese medicine, Tibetan medicine and Korean medicine.

Simple Sum-up and Make Mean Fade out the Important Changes, in a System Double-Blind and Cross Over

There are many experimental systems for evaluating QOL on the basis of western medicine. Almost all the experimental protocols are recommended to double blind and cross over system as a better

evaluating system. However, simple sum up and make mean for comparison of efficacy before and after the administrating some menu. Our evidence from light exercise, walking, hot spring hydrotherapy etc., we had no result by the method, making summing up and make mean in all the menu of CAM. For at least three types of individuals that responded to up-regulation, down regulation and no changed one. So simple summing up is cancelled the each vector of individual. The X-axis according to the value before each CAM menu. The data could represent by linear slant. The value correlation/tangent was representing the each result from CAM menu/walking. We tried to compare the best impact for each individual; we set up two sort of impact. The one was walking 4km/hrs (4mets), and the other was 8km/hrs (8mets) to the same volunteer at the different day after the cooling off from the former menu [1-3]. In order to establish some effect from each designed experiment, one usually recommended making experimental system as double blind and crossing over system. Hot Spring Hydro Therapy Regulate Peripheral Leukocyte Together with Emotional Hormone and Receptor Positive Lymphocytes According to Each Constitution/Condition is important to conscious of circadian rhythm. Abo reported that it was possible to sort the constitution, granulocyte-rich individual and lymphocyte-rich one with the peripheral leukocyte. Each population of subset is depending on a circadian rhythm. Within a same individual, granulocyte increase in the daytime, on the other hand, lymphocyte increased in the nighttime in a cycle 24 hrs. So we have to compare the effect of each menu for the peripheral leukocyte on the same time before and after the menu (Figures 1-4) [4-7].

Proposed Standard for QOL Assessment

The immune system is a totally integrative system. Professor Tada expresses this system as Super System. It includes brain, endocrine and immune system. For example, an immune system contains various cells, tissues and organs that protect organisms against potentially harmful pathogens from the external environment. The present concept of the word immunity has proposed considerably from its original definition to the standard scale for CAM (complementary and alternative medicine). Quite literally, its earlier usage referred to

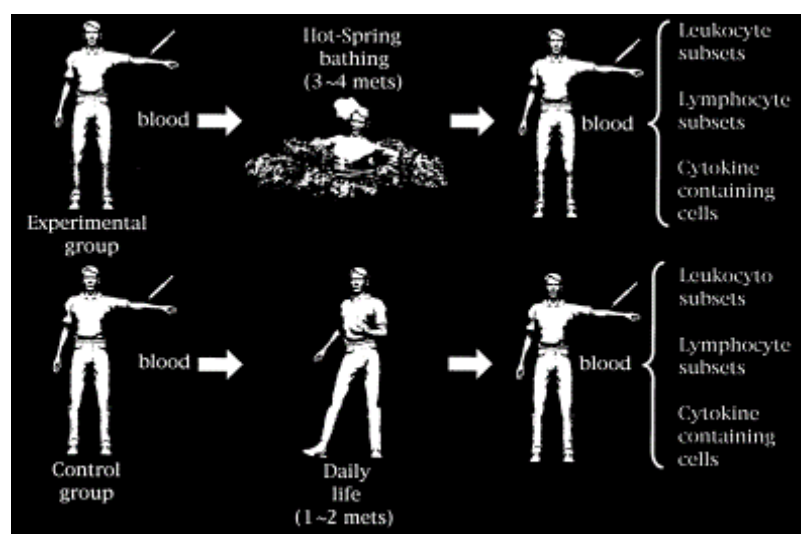


Figure 1: General experimental design to evaluate each CAM therapy. General style for the experiment was designed to collect factors before and after the CAM menu. However, the impotent sings to collect the factor have to keep the time lag is 24 hrs in order to avoid the circadian rhythm. 24 hrs change of leukocyte counts on the bases of group comparison between pre/post therapies. We sampled peripheral blood from each volunteer before and after CAM therapy, at the same time on each day, in accordance with the consideration of circadian rhythm of leukocyte in this figure, we tried to show the date simply pooled and make mean, and then compared.

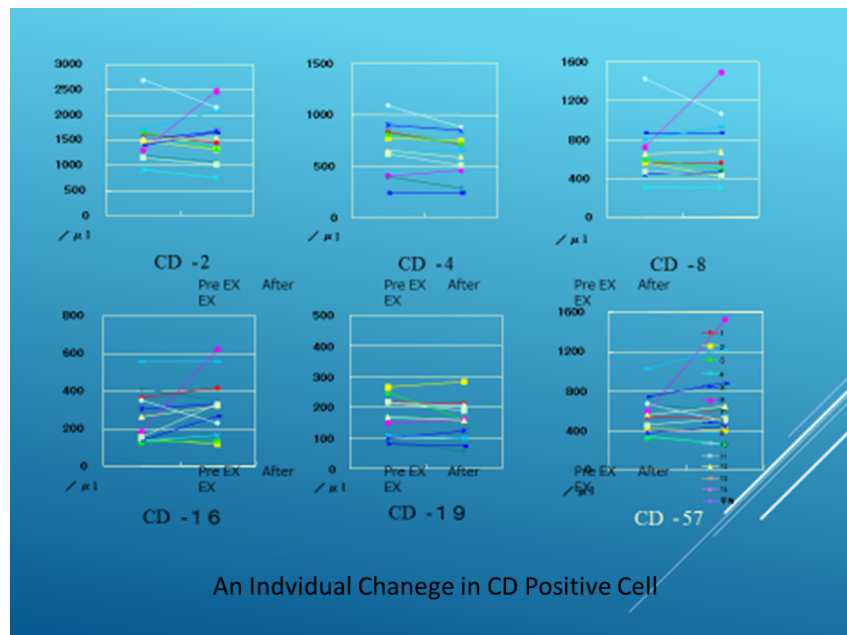


Figure 2: Simple and conventional presentation of the effect by walking, 4 mets. We first got the data from leukocyte regulation from 24 hrs interval. But there were many constitutional differences. For example, up-regulated group, down-regulated and no-changed group. So, in this presentation style, simple sum-up and make mean got the result as no change from this figure.

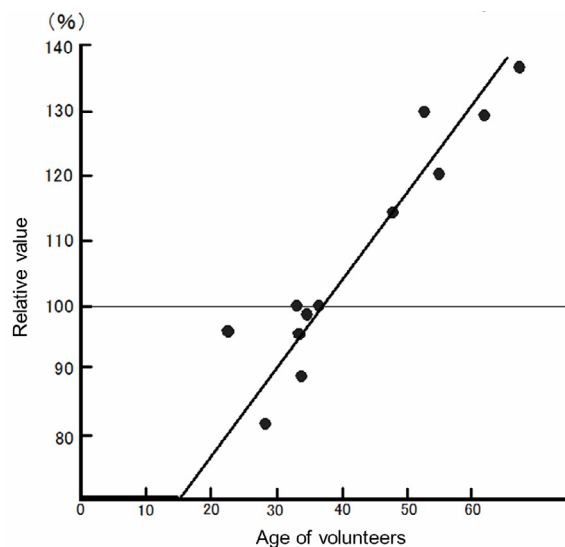


Figure 3: The constitution/condition dependent regulation and presentation by linear slant and judging by their tangent value/co-efficiency. A graphical presentation for the summary of the hot spring hydrotherapy. We tried to express the effect of peripheral total leukocyte number by individual level of change and plot in the X-axis as in each age. Variations in leukocyte subpopulations in the peripheral blood before and after each CAM therapy.

exemption from military service or the paying of taxes. Now, immunity not only “frees” one from disease but also the standard scale for CAM.

Physiological Super System: Immunological Network

The immune system shares with the nervous system at least two characteristics. The young individual is born with a certain potential to learn and to react to numerous and varied environmental stimuli both systems can lean. Once information is learned by the immune and nervous systems, it becomes in a sense imprinted, and each system retains the information in varying degrees, a process defined as memory. Despite the intense learning that young systems must do

subsequent to birth and will continue to do throughout their life time, infants are born into the world with certain innate behavior patterns controlled by the nervous system, and certain innate or characteristic natural immunities. Innate or natural, immunity includes all non-specific resistance or specific immune responses.

The Urgent Need for Alternative and Complementary Medicine Nowadays in All Over the World

Recently, alternative and complementary medicines together with oriental and traditional medicines have attracted much attention. This new interest includes aromatherapy and herbal medications,

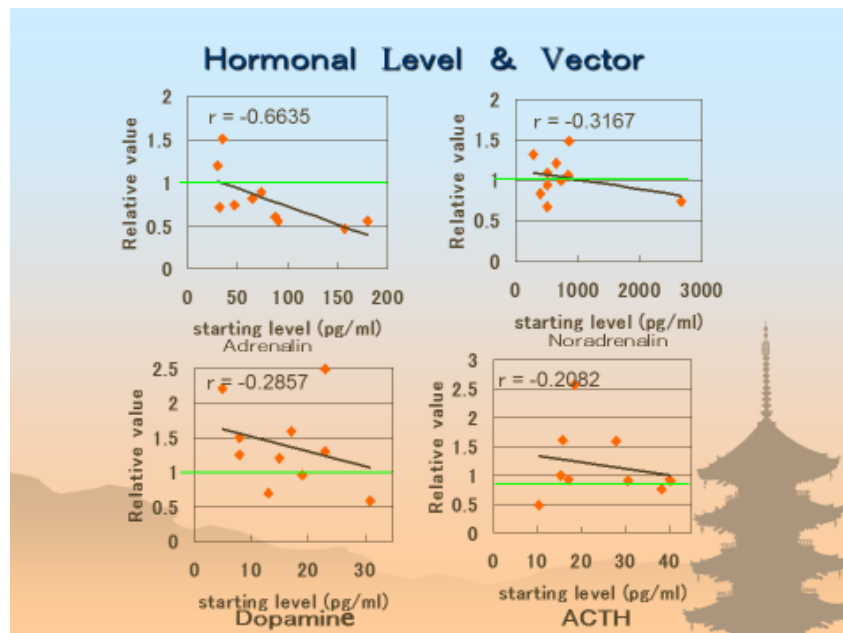


Figure 4: An emotional hormone also regulated by CAM therapy. The constitution dependent analysis for (adrenaline and dopamine). Each spot were obtained from the calculation comparing relative value from before and after levels in the serum, catecholamines levels in the peripheral blood within the figure, adrenalin and dopamine were regulated as was the same in leukocyte regulation. The clear slant was made from the data especially, in regulation in adrenalin; overall trend was decrease but was dose dependent manner of the value the day before. Also, dopamine was increased but also dose dependent manner as slant making.

acupuncture, moxibustion and yoga. However, these therapies have not been well defined. Some are simply based on legend or belief while others are traditionally applied but without scientific evidence. Then the assessment of each therapy and remedy need for their capacity through a scientific methods especially developed by Western Medicine. Although the word Alternative & Complementary Medicine is not popular enough in Japan than US and European countries, because in oriental countries so called Alternative and Complementary Medicine in Europe and north America is authorized medicine but not alternative one in the long histories in the world. Here I would like to introduce you where the alternative and complementary medicine now in Japan as well as in each country in the world is and where should it be going in the future.

What is the Alternative and Complementary Medicine in the East and the West?

The Japanese Alternative and Complementary Medicine Society define alternative and complementary medicine “the modern Western medicine which has not been verified scientifically and practiced at the daily clinic.” In the U.S., it is called the alternative medicine or the Complementary and Alternative Medicine (CAM). Anyway it is the medicine that is not lectured at the medical school and practiced at the daily clinic. The medicine can be classified into either the conventional medicine or the unconventional medicine. The conventional medicine is also called the modern Western medicine, scientific medicine or technical medicine, and the unconventional medicine is called the alternative, complementary, natural or fringe medicine. In Japan, the alternative medicine contains the traditional Chinese medicine, acupuncture and judo reduction etc. established as the Eastern medicine and they have their own independent long history. Since the herbal medicine is not insured in Japan, some insist it is not belong to the alternative medicine. However it is considered as alternative medicine in the West. Thus the position of the alternative medicine

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Alternative and Complementary Medicine in the Future

As we here took an overview about the today’s alternative and complementary medicine, I think it is high time this medicine should be standardized uniformly and Japan could play an important roll in this task. In Japan, the Eastern Medicine especially the herbal medicine (Kampo) was once the central medical care for long time until the Meiji Government decided to import the Western medicine as the ordinary medical care. Thus in Japan not only the Western but also the Eastern medicine could have been developed, and Japan now takes great pride in the longevity. This is why I suppose Japan should take the initiative for the standardization of the alternative and complementary medicine. The problem is how it should be standardized. Here I would like you to propose something. Most of the alternative medicine works through affecting the regularly system inside the body. For example, recent studies revealed the herbal medicine caused the interaction between the immune system, the endocrine system and the nervous system. Therefore observing the immune system by like sampling the peripheral blood might be an indicator for the standardization of the alternative medicine. Due to the above difficulties, this realm of medicine has often been shut out of the serious journals of western medicine. A new Journal concerning around complementary, alternative and traditional medicine” will be launched in a desire to ameliorate this situation,

by encouraging the publication of original scientific papers based on sound scientific guidelines, but without prejudice against the possible efficacy of these new and ancient treatments.

Immune Componence as a QOL Factors

Non-granular leukocytes

Man, other complex vertebrates, and even many invertebrates have evolved a system of internal transport for communicating components of the immune system. It is the blood, within the circulatory system, that executes these tasks. The blood contains two major types of cells: erythrocytes, or red blood cells, and leukocytes, or white blood cells. Leukocytes play important roles in the immune system. There are two basic types of leukocytes: the non-granular and the granular. The non-granular (agranular) leukocytes are further divided into two types: lymphocytes and monocytes.

Lymphocytes possess antibody receptors for antigens on their surfaces, and are thus vital to specific immune response throughout the entire body, where they freely move about. Monocytes are produced in the bone marrow, but like other blood cells they are eventually found in the blood. They frequently exhibit amoeboid movement, and they are voracious phagocytes when they enter connective tissues as macrophages from the blood. Both are important for quick, on the spot, phagocytosis.

Granular leukocytes

Granular leukocytes include neutrophils, eosinophils and basophils. The number of neutrophils increases in infections; neutrophils are not neutral at the sidelines, but provide the first line of defense against invading foreign bodies and organisms. In allergies and parasitic infestations, the number of eosinophils increases. Basophils are important for the production of histamine, the primary cause of skin reactions in allergic responses. The “most phagocytic” of white blood cells are neutrophils and monocytes. This phagocytic property is largely manifest in the connective tissue. Both cell types ingest foreign particles, bacteria and degenerating cells and fragments, and are thus crucial to the body’s non-specific immune reactions. Such responses involve rapid elimination of foreign material and antibody is not necessarily involved. This is one feature of man’s immune system that is traceable in evolution to single-cell amoebae [8-22].

Phagocyte, Augmentation of Subcutaneous Macrophage

Phagocytosis, the process of ingesting foreign material, is a non-specific immune reaction without the usual aid of specificity accompanying immunoglobulin or antibody synthesis. Macrophages and neutrophils will engulf almost anything (they are not as discerning as lymphocytes). To verify the presence of phagocytic cells one need only inject an animal with carbon particles, and shortly thereafter phagocytes are blackened, heavily engorged with the ingested particles. Phagocytosis can contribute significantly to an animal’s resistance to infectious organisms. When the macrophage engulfs antigen (e.g. foreign particles or infectious organisms) it is then ready to be processed, setting in motion a chain of events that begins a specific immune response. That processed antigen is somehow made “palatable” to sensitized lymphocytes, some of which then differentiate to plasma cell specific for that antigen. With another physiological function, macrophage respond wax substance that is composed in tuberculin bacilli, difficult to digest in his cytoplasm. When he meets this substance, he tried to his bet for digestion, resulting many kind of cytokine for surrounding. This condition leads to accelerate the dynamic for his subcutaneous. In such

mechanism, solubilized wax substance promote skin turnover, some kind of cosmetics for lady [23-31].

T cells, B cells

Differentiated lymphocytes must first originate from some primitive source or stem cell which resides in the bone marrow. Further differentiation leads to the development of lymphoid stem cells that are destined for “education” in two sites. It is believed that, through migration, they enter the thymus in mammals and birds and end up as T-cells (lymphocytes) that effect cell-mediated responses.

Another population develops in situ into B-cells in mammals, or in birds they pass through the avian bursa of Fabricius to become B-cells, differentiate into plasma cells, and thus are capable of effecting humoral immune responses. Speculation in the past assigned the mammalian equivalent of the avian bursa of Fabricius to gut-associated lymphoid tissue, including the appendix and Peyer’s patches. Although not completely resolved, the generally accepted view is that the bone marrow possesses the greatest concentration of B-lymphocytes. Plasma cells which develop from stimulated B-cells are most active in antibody synthesis. In the serum, immunoglobulin levels generally correlate well with increased numbers of plasma cells in germinal centers of lymphoid nodules (lymph nodes, spleen). The thymus has no B-cells, no germinal centers, and therefore produces no antibody.

The Two Types of Immunity

Cellular immunity is functionally related to the immune activity of cells of the immune system, particularly T-cells, whereas humoral immunity emphasizes the products of B cells, or antibodies. For cells of the immune system to recognize not-self they must bear recognition units. Such units, or receptors, are antibody, found on the surface of B-lymphocytes. The nature of T-cell receptors is a matter of much debate. These surface patches of antibody are the “eyes and ears” of lymphocytes, rendering them capable of detecting antigen. After sensitive lymphocytes either select or are selected by antigen they are triggered/stimulated, able to reproduce their kind, leaving descendants ready for a second, faster reaction to the same antigen should it be encountered. This states in very simple terms the clonal selection theory of antibody synthesis. In other words, the fittest lymphocytes, due to the presence of receptors, will survive. It is believed that the immune system, acting as an immunologic surveillance system, evolved to police the surfaces of self-cells and to readily dispose of those which maybe antigenically changed and are therefore not-self. According to this view, such cells could become cancerous and thereby would interfere with effective survival. In this way the immune system functions as the body’s guardian against internal threats; its role in external threats is clear.

Antigens

To begin an immune response, immunologically competent lymphocytes with receptors must make contact with antigen. Antigens are any of various kinds of chemical substances capable of stimulating an animal’s immune system to produce antibody or Cell mediated immune reactions. Starting with the response to antigen, and until the final product, antibody, is synthesized, we can observe an amazing specificity. Specificity is revealed by the capacity of antibody, directed against a particular determinant of an antigenic molecule, to react only with this determinant or another closely related one. The antibody response to a given antigen specific that even minor alterations in the determinant, or that portion of the molecule responsible for its antigenic properties, marked alter the ability of the determinant to

react with antibody. Antigens can be soluble or particulate soluble antigens are substances such as proteins (e.g. egg albumin). Foreign erythrocytes or bacteria are examples of particulate antigens that stimulate cells to evoke humoral immunity (antibody synthesis), when individuals receive a smallpox immunization, they are receiving an antigen that induces antibody, and as a result they are immune. Smallpox immunizations have virtually eradicated the disease. Once these kinds of antigens enter an animal a chain of events is set in motion resulting in antibody synthesis.

Crucial Definition of Immunity

Cellular antigens such as those on tissue grafts stimulate cells to produce lymphokinesis that act locally to destroy the perturbing antigen. Inherent to humoral and cellular immune responses is specificity and memory. Antigen administered for the first time initiates a primary immune response. In this case, antibody is at low levels and does not persist for long periods, unless a second dose of antigen is administered. If this happens, in a very short time even after one day-a spectacular rise in antibody takes place; the level attained is higher than that of the primary response antibody, and the level is reached more rapidly. This Secondary response antibody remains at a high level for a longer period than does the primary. Long-lasting immunity is due to the antibody that remains after periodic boosters to such antigens as smallpox. Thus, the immune system, with its specificity and memory, ensures a rapid production of antibody and elimination of antigen after a second encounter. Memory resides in those long-lived lymphocytes capable of continued reproduction.

The Immunoglobulins

There are five classes of antibodies (IgG, IgM, IgA, IgD, IgE) Immunoglobulin G or IgG, antibodies consist of a single unit of two short ("light") chains, and two long("heavy") ones. Each of the others is structurally similar, but they are all functionally different. IgG, the most common form of antibody passes from mother to fetus before birth in most individuals, it is present in high concentration in the blood only after prolonged exposure to antigen, and thus it represents the bulk of normal immunoglobulin in human blood. In contrast to IgG, IgM appears early after exposure to an antigen, but does not cross the placenta to an unborn child. Since it has five of the basic double-chain structures, it can combine with antigen at more than one site, and is thus more effective both in neutralizing certain antigens like viruses and in combining with others like bacteria. Apparently, the specificity of IgM for antigen determinants is not as great as that of IgG; thus its action in neutralizing certain harmful toxins is less effective than that of IgG. Like IgG, IgM can readily act element, and therefore it plays an active role the induction of lysis of certain foreign cells. IgM is also effective in antigen agglutination and opsonization, a process that prepares particles for phagocytosis here are two forms of IgA. Secretory IgA is resistant to proteolytic enzymes, or those enzymes that dissolve proteins or peptides into simpler, soluble products. By means of this resistance, a part of its structure the secretory piece may confers stability on the molecule, preventing its breakdown in potentially hazardous areas such as the gut. Thus, secretory IgA actually represents a second line of defense after the epithelial surfaces of mucous membranes, and is of special importance, therefore, in providing protection against antigens invading the respiratory tract. Little is known about IgD. It was first observed in patients with a kind of cancer called multiple myeloma. It has since been found in very small quantities in normal serum, but its specific biologic role is yet to be defined. IgD is also known to occur in patients with specific diseases, often associated with a malfunctioning immune system (e.g. systemic

lupus erythematosus and rheumatoid disease). It increases during pregnancy and is often elevated in patients with allergies. IgE is of great clinical importance since it has been determined that antibodies of this class, when combined with antigens, are responsible for severe and acute allergic reactions. Although the concentration of IgE in normal blood serum increases with time in childhood, it generally remains low, except in persons with various kinds of allergies.

Clinical Aspects of Immunology-Hypersensitivity

Everyone is familiar with the best known of all immunological diseases, the allergies-usually called "hypersensitivities" by physicians. When an individual has been immunologically primed, or sensitized, to an antigen, either deliberately (as in vaccines) or naturally, further exposure at a later date does not always lead to a booster effect of the immune response (memory), but quite the opposite, tissue-damaging reactions can also occur. Some hypersensitivity reactions are immediate and dramatic, such as sensitivity to insect stings or to drugs such as penicillin. If an acute generalized reaction is not promptly treated, death will occur. Less serious allergic reactions occur in persons sensitized to grass pollens, animal dangers, house dust, etc. In all such reactions contact of the allergen with IgE antibodies releases chemical mediators from basophils and mast cells (e.g. histamine), which produce the typical symptoms of allergy-sneezing, wheezing, runny nose and 'teary eyes. This type of sensitivity can be passed to normal individuals by injecting serum containing the IgE or skin sensitizing antibodies.

Acquired Immuno-Suppression

It may be desirable to suppress the immune response when an individual is to be the recipient of a transplant. At the present time, host-donor matching is limited and must be supplemented by immunotherapy designed to suppress the host's immune response. Suppression is usually accomplished by chemical and physical means (irradiation), employing the same drugs often used in cancer chemotherapy; both cancer cells and immune cells actively divide. In general, those drugs often anti-metabolites that interfere with nucleic acid or protein synthesis can suppress the immune response. The greatest problem facing the physician is to effectively balance at the same time the dosages of drugs or irradiation so that the immune system is suppressed against the graft, but is still capable of defense against environmental pathogens [32-42].

Tumor Immunology-Special Reference to Mal-Surface Antigenicity

In addition to the above-described classic components of the immune response to cancer, it has recently become clear that there is a family of natural immune effector mechanisms that may also play an important role in resistance to tumor growth. In contrast to specific T- and B-cell-mediated immunity' which is not present in normal individuals and develops after a latent period of one to two weeks after sensitization by TAA, natural immunity is present spontaneously in normal individuals and does not depend upon exposure to tumor cells.

The natural immune system is a multifaceted compartment, including macrophages, Natural Killer (NK) cells and related cytotoxic effector cells, granulocytes, and natural antibodies. Since natural immunity exists prior to the development of tumor cells, and since its activity usually can be augmented very rapidly (within hours to days after certain stimuli), it has been suggested that these components of the immune system may form the first line of defense against tumor cells and other foreign materials such as microbial agents.

Monocytes and macrophages from normal individuals may have spontaneous cytotoxic reactivity against a wide variety of tumor cells. Upon activation by various signals, par T-cell-mediated lymphokine, activating factor, and inter cells can become highly cyto-reactivity against tumor cells particularly the macrophage interferon, these toxic. Their does not appear to depend on recognition of TAA's (tumor associated antigens) but rather on recognition of some cell surface structures that are expressed on a large proportion of tumor cells and that are usually undetectable on normal cells of the same individual. This allows activated monocytes and macrophages to exert strong, selective killing activity against tumor cells and to leave surrounding or adjacent normal cells unharmed.

NK cells were discovered about ten years ago as lymphoid cells with spontaneous cytotoxic activity against many tumor cells. For quite some time, their characterization was elusive, and it could be stated only that they lacked the characteristic features of macrophages, T-cells, or B-cells. Recently, however, it has been found that a small subpopulation of cells, termed large granular lymphocytes (LGL) and representing about 5 per cent of the mononuclear cells in human or rodent blood or spleen, account for virtually all of the NK activity. These LGL are morphologically distinguishable from typical lymphocytes, having a kidney-shaped nucleus and more abundant cytoplasm and numerous azurophilic granules, and, by virtue of their lower density, can be highly purified. NK cells, in contrast to cytotoxic T-lymphocytes, react with tumor cells independently of MHC antigens but rather appear to recognize a few broadly distributed target cell structures. Although NK cells primarily react only with tumor cells, they have been found to also lyse small subpopulations of normal cells, especially undifferentiated cells in the thymus or bone marrow or embryonic cells. The activity of NK cells can be rapidly increased by treatment with interferon or interferon-inducers and, on the other hand, can be inhibited by prostaglandins of the E series and by certain macrophages or T-suppressor cells. Natural and antitumor antibodies are also widely expressed in the sera of normal individuals. These provide yet another possible mechanism for interaction with tumor cells. As described earlier for immune antibodies, they might have direct complement-dependent cytotoxic effects or they might be involved in ADCC reactions against tumor cells. The defense of a host against tumor invasion is thought to depend in part upon its immune system. Clearly the immune system is involved in the body reaction to tumors. Three fundamental factors of tumor immunology have been shown in laboratory animal-models to interact with and to in nuance each other in the progression or regression of tumors. These three factors which determine survival or death consider: (1) That antigens are present on the surface of tumor cells; (2) That lymphocytes and macrophages to attack the tumor can be developed; (3) That humoral antibodies capable of affecting both the tumor and the attacking host cellular elements can also be developed. Hence, tumor cells are close character to embryonic stem cell, therefore the specific antigenicity IA not develop in surface especially MHC antigen. In this case, natural killer cells are expected to attack to the corresponding tumor cell. Recently, extrinsic factor to guide the tumor cell to suicide, autophagy and/or apoptosis. The name of agent is Cordecepin. This component is one of the constituent of *Cordeceps* spp. that was known as a special mushroom grown up to the dead larvae of some kind of moss originally succeeded in Himalayan highland. This special mushroom had been famous for food additive for recovery of the exhaustion for over the centennial. Recently many reports have been published that the Cordecepin help suicide to corresponding tumor cell *in vitro* and/or *in vivo*. Hence naturally made *Cordyceps* spp. is expensive in the market so that cultured species, *Cordyceps militaris* is easy to pick up to the

sample of the laboratory that evidenced by selective toxicity for many kind of tamer cell as in animal as human cell line [43-70].

Acquired Immunodeficiency, Diseases and Autoimmunity

The immune system is divided morphologically and functionally into three types: (1) The phagocytic system (macrophages, granulocytes); (2) The T-cell system develops under the influence of the thymus and functions chiefly in cell-mediated immunities that do not involve antibodies; (3) The B-cell system is derived in humans from the equivalent of the avian bursa of Fabricius (probably the bone marrow) and such cells secrete antibody, their role in humoral immunity. T-lymphocytes can also cooperate with B-Lymphocytes and macrophages synthesize antibody. Without the phagocytic system an individual will die of infections. When either of the other two systems is defective, immunodeficiency diseases result. For example, in the Di- George syndrome patients may be born without a thymus, and, in the absence of T-cells, such patients cannot reject solid tissue allografts or develop delayed hypersensitivity responses. However, they possess normal or increased numbers of plasma cells, characteristic of a functioning B-cell system. In contrast to a T-cell deficiency, there is a disease due to absence of the B-cell system, a sex linked infantile immunodeficiency' characterized by the almost complete absence of plasma cells, germinal centers and the ability to form antibodies and immunoglobulins; however, the cell-mediated immune apparatus that destroys solid tissue allografts or that mediates delayed-type hypersensitivity is intact. In other in both the T- and B-cell leaving the patients infectious microorganism deficiency diseases may be affected.

Aging and Autoimmunity

As one undergoes senescence, there are major components of the entire process that reflect a general decline in immunologic vigor. When this occurs, individuals become more vulnerable to certain infections, malignancy and autoimmunity. The mechanism of autoimmunity and its relation to immunologic imbalance is extremely interesting. Under normal circumstances individuals are tolerant to self-components. If and when this tolerance breaks down, individuals may develop autoimmunity. Clearly autoimmunity occurs more frequently in patients with primary immunodeficiency than in most individuals. Auto-immunity in immunodeficiency disease, or in individuals whose immune apparatus is intact, may be related to the entry of forbidden antigens rather than the entry of forbidden (non-self) clones of cells. However, another possibility was that maternal cell enters into via placenta and modified the immune reactivity of her child. This maternal immunity to her young is another possibility of autoimmune disease and atopic hypersensitivity [71,72].

The Complement System

Activation of the complement system results in a cascade of interactions of these proteins, leading to the generation of products that have important biologic activities and that constitute an important humoral mediator system involved in inflammatory reactions. First, coating of particles, such as bacteria or immune complexes, with certain components of complement facilitates the ingestion of the particle by phagocytic cells (opsonic function of complement). Second, the activation event generates many fission products of complement proteins for which specific receptors exist on a variety of inflammatory cells, such as granulocytes, lymphocytes, and other cells. Binding of these complement-derived products to-such receptors results in biologic activities such as chemotaxis and hormone-like activation of cellular functions (inflammatory function of complement).

Pathways of Complement Activation and Complement Proteins

Activation of complement can occur by two separate pathways: The classical and the alternative pathways. Both pathways lead to a common terminal pathway referred to as the pathway of membrane attack. Twenty plasma proteins are now known to be constituents of these pathways. These proteins can be divided into functional proteins, which represent the elements of the various pathways, and regulatory proteins, which exhibit control function. The concentration of the proteins in normal human plasma covers a broad range. They are synthesized in the liver but also by cells of the lymph reticular system, such as lymphocytes and monocytes. Both the classical and the alternative complement pathways can be organized into various operational units: initiation, amplification, and membrane attack. Following an initial recognition event, which leads to initiation of the pathway, an amplification phase takes place that involves the action of proteases and the recruitment of additional molecules; this is followed by a terminal phase of membrane attack during which the cell dies. The recognition unit for the classical pathway, C1, is composed of three separate proteins, C1q, C1r, and C1s. The initiation of this pathway of complement typically involves the reaction of antibody with antigen, which may be soluble or on the surface of a target cell. This antigen-antibody reaction allows the binding of C₁q to two or more Fc regions of certain IgG subclasses (IgG1, IgG2, IgG₃) or IgM. Activators of the classical pathway. The ultra-structure of C₁q has been demonstrated by electron microscopy to consist of six subunits similar to a bouquet of six flowers. The central stalks of C₁q resemble collagen in primary and secondary structure. Upon binding of one C₁q molecule to the Fc regions of two or more antigen-bound antibody molecules, C₁r proenzymes are activated. The chemical basis of this activation is the cleavage of a peptide bond by an autocatalytic mechanism, leading to the formation of activated C₁r, a protease that subsequently cleaves the proenzyme C₁s. Thus, the binding of C₁q to an immunoglobulin in complex with the antigen represents the recognition event of the classical pathway, resulting in the activation of C₁r and C₁s. The final result is the generation of an enzymatically active component, C₁s, which will cleave and thereby activate the next proteins in the cascade, leading to amplification of the recognition event. The enzyme C₁s has two physiologic substrates, C4 and C2. C4 is cleaved by C₁s into C4a, one of the three anaphylatoxins (molecules that promote increased vascular permeability and smooth muscle contraction), and C4b, which binds to the target cell surface. C₁s also cleaves C2 when C2 is in complex with C4b. Cleavage of C2 generates C2b, which is released, and C2a, which remains bound to C4b. The bimolecular complex C4b, 2a is a protease that cleaves C3 and therefore is called C3 convertase. Cleavage of C3 by the C3 convertase generates two important biologically active peptides, C3a (another anaphylatoxin) and C3b, which attaches to target cell surfaces and can bind to C5. C5, when in complex with C3b, can be cleaved by the C3 convertase (then referred to as C5 convertase). The C5 convertase hydrolyzes C5, which generates the C5a anaphylatoxin and C5b. C5b is the nucleus for the formation of the membrane attack complex. Immediately following their generation, C3b and C4b exhibit a unique transient ability to covalently bind to target cells ("metastable binding site"). This property has recently been shown to be due to an intramolecular thioester bond that is present between the sulfhydryl group of a cysteine residue and the gamma carbonyl group of a glutamine residue on C3 and C4. Upon activation of C3 or C4, this thioester becomes highly reactive and can react with a cell surface hydroxyl or amino group. This results in the covalent attachment of C3b or C4b to the target cell. An additional function of

the thioester bond is its hydrolysis by water, occurring during activation of the alternative pathway as described below. The alternative pathway can be activated when a molecule of C3b is bound to a target cell. This C3b molecule combines with the plasma protein Factor B, which is a zymogen, and which, when bound to C3b, can be activated by the plasma protein Factor D by cleavage into two fragments, Ba and Bb. The Bb fragment, which contains the active enzymatic site, remains bound to C3b, as C3b, Bb. This complex, like C4b, 2a in the classical pathway, is a C3 convertase (C3b, Bb); it is stabilized by the binding of another plasma protein, properdin. Thus, the alternative pathway used to be called the properdin pathway. The presence of a single molecule of C3b generates many molecules of C3b, Bb, resulting in a tremendous amplification. The C3 convertase (C3b, Bb) cleaves C3, thereby generating more molecules of C3b, which can combine with other molecules of factor B to give more molecules of C3b, Bb, which can, in turn, cleave more molecules of C3. Therefore, the central feature of the alternative pathway is a positive feedback loop that amplifies the original recognition event. As in the classical pathway, attachment of many C3b molecules to the target cell will allow binding of C5 and its cleavage into C5a and C5b by the enzyme C3b, Bb, now referred to as C5 convertase. Owing to the potential of this positive feedback loop to rapidly use up Factor B and C3, the positive feedback must be carefully regulated. There are two important regulatory proteins in plasma. The first protein, Factor H (formerly referred to as PIH), competes with Factor B for binding to C3b and also dissociates C3b, Bb into C3b and Bb. The second control protein, Factor I (formerly referred to as C3b inactivator), cleaves C3b that is bound to Factor H or to a similar protein found on the surface of the host cell. The resulting cleaved C3b, termed iC3b, can no longer form a C3 convertase. The action of these two control proteins prevents the consumption of Factor B and C3 in plasma; in addition, these two proteins inactivate C3b, Bb on host cell surfaces. In contrast, surfaces of many target cells, such as bacteria and other microorganisms, protect C3b, Bb from inactivation by Factors H and I. This protection allows the positive feedback loop to proceed on the surface of the target cell, leading to the activation of the pathway and subsequent cell death. In other words, the alternative pathway is activated by those substances that prevent the inactivation of the positive feedback loop enzyme C3b, Bb. A substance is therefore treated as "foreign" if it restricts the action of Factors H and I and allows the positive feedback loop to continue. The chemical structures on surfaces of particles and cells responsible for activation or non-activation of the alternative pathway have not been identified. There is some evidence that carbohydrate moieties are involved, particularly sialic acid. The alternative pathway protein(s) responsible for the recognition of these structures also remains to be determined. As pointed out earlier, the activation of the alternative pathway requires a C3b molecule bound to the surface of a target cell. An intriguing question is, "Where does the critical first C3b molecule come from?" Although it can be provided by the C3 convertase of the classical pathway or by cleavage of C3 by plasmin and certain bacterial and other cellular proteases, the alternative pathway can generate this first C3b molecule without these proteases. The intramolecular thioester, which is highly reactive in nascent C3b and is responsible for the covalent attachment to targets, is also accessible in native C3 to water molecules. Thus, spontaneous hydrolysis of the thioester bond occurs constantly in plasma at a low rate. The C3 molecules in which the thioester bond has been hydrolyzed behave like C3b, although the C3a domain has not been removed. C3 with a hydrolyzed thioester is called C3(H₂O) or C3b-like C3. It can bind Factor B and allow Factor D to activate Factor B, which results in formation of a fluid-phase C3 convertase, C3(H₂O), Bb. This enzyme is continuously formed and produces C3b molecules that can randomly

attach to cells. Although these C3b molecules will be rapidly inactivated on host cells by Factors H and I, they will start the positive feedback loop on foreign surfaces, as outlined previously. In other words, the alternative pathway is constantly activated at a low rate, but amplification with subsequent cell death occurs only on foreign particles.

Products of Complement Activation Possessing Biological Activity

Activation of either the alternative or the classical pathway results in the generation of many important peptides involved in inflammatory responses. The anaphylaxis increase of vascular permeability degranulation of mast cells and basophils with release of histamine Degranulation of eosinophils Aggregation of platelets opsonization of particles and solubilization of immune complexes with subsequent facilitation of phagocytosis Release of neutrophils from bone marrow resulting in leukocytosis Smooth muscle contraction Increase of vascular permeability Smooth muscle contraction Increase of vascular permeability Degranulation of mast cells and basophils with release of histamine Degranulation of eosinophils Aggregation of platelets Chemotaxis of basophils, eosinophils, neutrophils, and monocytes Release of hydrolytic enzymes from neutrophils Chemotaxis of neutrophils Release of hydrolytic enzymes from neutrophils Inhibition of migration and induration of spreading of monocytes and macrophages anaphylatoxins C3a, C4a, and C5a are derived from the enzymatic cleavage of C3, C4, and C5 respectively. Historically, C3a and C5a were defined as factors derived from activated serum possessing spasmogenic activity. The anaphylatoxins are now recognized as having many additional biologic functions. Both C3a and C5a are known to induce the release of histamine from mast cells and basophils (chapter 20A). As shown in Figure 4 both anaphylatoxins cause smooth muscle contraction and induce the release of vasoactive amines, which cause an increase in vascular permeability. The effect of C5a anaphylatoxin on neutrophils is of considerable importance in the inflammatory response. Not only can C5a induce neutrophil aggregation, but this anaphylatoxin appears to be the main chemotactic peptide generated by activation of either complement pathway. *In vitro*, Nano molar concentrations of C5a will induce the unidirectional movement of neutrophils. Other inflammatory cells, such as monocytes, eosinophils, basophils, and macrophages, have also been shown to exhibit a chemotactic response to C5a. The removal of the carboxy-terminal arginine from C5a by serum carboxyl peptidase N, generating C5a-des-arg, inactivates the spasmogen, yet restoration of full chemotactic activity of C5a-des-arg may occur in the presence of serum. Therefore, C5a-des-arg may also be responsible for *in vivo* neutrophil chemotactic activity. As described earlier, the cleavage of C3 by either the alternative or the classical C3 convertases results in the production of two major split products, the C3a anaphylatoxin and C3b. The larger C3b fragment can serve as an opsonin (promoter of phagocytosis) by binding to a target through the thioester mechanism. This renders the particle or cell immediately susceptible to ingestion by a variety of phagocytic cells that carry specific receptors for C3b. Many recent observations point to additional roles for complement fragments in regulating the activity of cells of the immune system. These observations include the presence of receptors on lymphocytes for various complement proteins, including C3 split products and Factor H, affecting B- and T cell function. This is an important area for future research [73,74].

The Pathway of Membrane Attack Complex

The formation of C5b by the classical or alternative C5 convertase

marks the initiation of the membrane attack pathway. Nascent C5b can bind to C6, resulting in the formation of the stable C5b,6 complex. Subsequently C5b,6 reacts with C7 to form the trimolecular complex C5b,6,7, which exhibits a metastable binding site through which the complex can bind itself to the target cell membrane. Although the exact biochemical nature of this metastable binding site is unknown, it is believed that binding occurs through hydrophobic interactions with membrane lipids. Next, binding of C8 to the C5b, 6, 7 complex occurs on the cell membrane, which causes the transposition of C9 from the plasma into the target cell membrane by inducing a polymerization of C9. The polymerization of C9 in the membrane occurs typically in a circular fashion, inserting poly C9 cylinders consisting of about 12 to 16 C9 molecules. The poly C9 cylinders are responsible for the characteristic ring-like appearance of the complement lesions seen by electron microscopy. The poly C9 with the attached C5b, 6, 7, 8 complexes is usually referred to as the membrane attack complex (MAC). It has been established that the membrane lytic action of the MAC is due entirely to physical interactions. The MAC is a hollow structure with an inner diameter of 100 Å; therefore, its insertion into the membrane results in transmembrane channels that are large enough to allow molecules the size of proteins to pass through. In addition, the strong lipid-binding capability of the MAC results in disorganization of the phospholipid layer, causing impairment of membrane function. In the case of gram-negative bacteria, the peptidoglycan layer prevents MAC mediated lysis. However, these bacteria are killed by the insertion of the MAC into the outer membrane. Lysis of these bacteria requires the presence of lysozyme, which can leave the peptidoglycan.

Regulatory Mechanisms of Complement Cascade-Fermented oligo-saccharide hits Alternative Pathway

Activation of the complement cascade results in a complex series of molecular events with potent biologic consequences. Accordingly, modulating mechanisms are necessary to regulate complement activation and to control the production of biologically active complement products. The first mechanism by which the activity of many activated complement components is modulated is spontaneous decay. Examples of this mechanism are the transient stability of the activated thioester bond in C3b and C4b, and the short half-life of the enzymatically active complexes C4b,2a and C3b,Bb. The second type of regulatory mechanism is the inactivation of certain components by proteolytic enzymes. For example, the plasma protease Factor I can, in the presence of certain cofactors (see below), inactivate C3b and C4b. A major mechanism for controlling the biologic activity of C3a and C5a anaphylatoxins is serum carboxypeptidase N, as described earlier. Another control protein that may exert a regulatory effect on the C5a anaphylatoxin is the chemotactic factor inactivator. Although the chemical basis of the inactivation is not known, this serum-derived factor appears to irreversibly inactivate many of the biologic activities of C5a. A third mechanism of regulation involves specific binding proteins that modulate the activity of certain complement components. Examples are Factor H and C4b-binding protein, which, when bound to C3b and C4b, respectively, make them susceptible to cleavage by Factor I. Another example is S-protein, which binds to the MAC if the MAC is assembling in plasma rather than on a target cell. Binding of the S-protein to the MAC abrogates its ability to attach to a cell membrane, thus limiting attachment of MAC to cells at the site of complement activation.

Another important binding protein is C₁ esterase inhibitor (C₁ INA), which regulates activation of the classical pathway by forming killer lymphocytes and helper T-lymphocytes. It is obvious that

most human patients with cancer of any sort possess specific cell-mediated immunity and specific antibodies against tumor-associated antigens (TAA) of their autochthonous tumors. It is not clear why, in those individuals with progressing or disseminating cancer, such demonstrable immune responses are not adequate to control the tumor; some of the probable explanations are described in later sections.

Other Factors Contributing to Illness

As a growing number of patients struggle with illnesses involving depressed immune function and overstressed hormonal and nervous systems, physicians must cope with the fact that these illnesses simply do not respond to the types of treatments being offered by conventional medicine today. To better understand this situation, we must first look at some of the factors influencing our health.

Genetics: From our parents we receive our genetic inheritance, and are born with constitutional strengths and weaknesses over which we have no control. External factors provide additional layers of influence which act on our genetically acquired ability to adapt and cope.

Diet: Emmanuel Cheraskin, M.D., D.M.D., of Birmingham, Alabama, pictures the sick individual as a layered “onion” whose signs and symptoms serve as the onion’s outer layers, with layers of biochemical imbalance lying underneath. At the core of the onion, according to Dr. Cheraskin’s research, lies poor diet. That diet is so essential to health is not surprising. The foods and liquids we consume, along with the air that we breathe, have a fundamental effect on our well-being. A healthy diet of pesticide-free fruits and vegetables whole grains, seeds, and nuts, along with organically raised, free-range poultry and certain types of fish, can supply us with all of the essential nutrients our bodies require for optimum efficiency, energy, and freedom from disease. Such a diet is rare today, however, having been replaced by foods high in unhealthy levels of fat, preservatives, chemical additives, and, in the case of most of the meat available in the United States, antibiotics and hormones, due to the way our livestock is raised. These factors alone can contribute too much of the chronic ill-health conditions besetting people today.

Mental and emotional stress: Research in the field of mind/body medicine has revealed that there is a direct link between mental and emotional distress and the body’s ability to resist illness. It has also been discovered that unresolved or unexpressed thoughts and feelings are translated in the body as neurochemicals. These chemicals communicate with other systems of the body, particularly the autonomic nervous system, causing the body to react in a manner similar to when physical stress is present. Fear, for example, arouses the nervous system and triggers a flood of adrenal hormones, causing an accelerated heart rate and intensified breathing. Under healthy conditions, such reactions soon subside, but chronic fear, anger, grief, and other powerful emotions can keep the nervous system in a constant state of arousal. This allows stress to build up in the body, eventually attacking the body’s organs and resulting in depressed immunity.

Environmental pollution: Pollutants in the air, water, soil, and the foods we eat can contribute to illnesses ranging from birth defects and cancer to Alzheimer’s disease. They also can create a severe toll on the immune system, leading to many other chronic conditions, such as allergies.

Dental factors: The relationship between common dental silver amalgam fillings and chronic illness is now becoming recognized by a growing number of dentists, physicians, and researchers. The problem lies with the fact that calling the fillings silver is a misnomer because

they are actually composed of 50 percent mercury, one of the metals most toxic to the human body. Over time, the mercury can slowly leech out of the fillings. When this happens, damage may occur to the nervous system, leading to symptoms resembling multiple sclerosis, chronic fatigue syndrome, and senile dementia. Infections in the gums can also diminish health by suppressing immune function and increasing the susceptibility of disease elsewhere in the body. The misalignment between the skull and jaw caused by temporomandibular joint syndrome can also create various types of stress that can result in depression, insomnia, headaches, fatigue, chronic pain, and low back pain.

The inappropriate use of antibiotics: Antibiotics are valuable drugs when they are used appropriately. But the evidence today points to massive overuse. Antibiotics are often prescribed for medical conditions that do not warrant them. For instance, they are routinely given for colds, but many colds are the result of viral infections, and while antibiotics kill bacteria, they have no effect on the viruses. The use of antibiotics can also result in a variety of side effects due to the way their powerful actions can interfere with the delicate balance of the body’s systems. This can result in the destruction of the friendly bacteria in the body, leading to yeast overgrowth, both locally, such as in vaginal infections, and systemically, in the form of candidiasis; interference of nutrient absorption, the development of food allergies; recurrent ear infections, and immune suppression, as evidenced by the large percentage of adults suffering from chronic fatigue syndrome who have histories of recurrent antibiotic treatment as children or adolescents.

Electromagnetic Fields (EMFs): Electromagnetic Fields (EMFs) are invisible yet active forces produced by electrical appliances (including computers, microwave ovens, and even electric razors), power lines, and wiring. Researchers have only recently begun to realize the effects EMFs can have on health. Recently, the Special Epidemiology Studies Program of the California Department of Health Services noted that EMFs can, in fact, change biological tissue; although the full range of their health effects remain unknown. Additional studies by the United States Environmental Protection Agency have found that, in the last twenty years, possible associations have been found between EMFs and miscarriages, birth defects, leukemia, brain cancers, and lymphomas.

Geopathic stress: Geopathic refers to illnesses that are caused, or contributed to, by areas of harmful radiation from the earth itself. That such a possibility exists has been known to traditional cultures for thousands of years. The Chinese art of Feng-shui (the study of subtle earth energies and their relation to human life), for instance, takes into account the effects of harmful radiation from the earth to safeguard against building over the locations from which they emanate. According to Anthony Scott-Morley, D.Sc., Ph.D., M.D. (alt. med.), of Dorset, England, as many as 30-50% of the chronically ill exhibit some signs of Geopathic stress. These include excessive sleeping, cold extremities, respiratory difficulties, and unexplained mood changes and depression.

The Role of Oriental Pharmacology for Western Therapeutics in Cancer: For Maintain the Basic Infectious Immunity

Although the law specifies that a clinical trial is required to demonstrate a drug’s efficacy, we have seen how fundamental research influences the perception of a drug. As a result of such perceptions, animal fundamental research has assumed considerable importance in the thinking of western physicians. Thus, just as animal pharmacological

studies are an essential part of predicting whether a potential new drug will be effective, the western tradition of medical training assumes that the study of animal pharmacology is the basis of medical therapeutics. In other words, the guide line derived from animal testing establishes the credibility of a potential new drug both in the drug development process and in aiming the attitudes of western medicine. On the contrary, Herbal remedy medicine has developed from clinical experience and theories that do not depend on animal experiments. Recently, have western pharmacological and chemical methods been used to examine whether Herbal remedy medicines may have special properties. Some pharmacological studies are interesting because they employ the methods of modern pharmacology to guide to the view that an ancient crude herbal prescription may have special properties not found simply in its "active principle." Furthermore, such studies remind us that some useful drugs were available in oriental countries before the development of the pharmacological paradigm and therefore that useful ideas for drugs may arise outside this paradigm. Indeed the reliance of western drug development on animal pharmacological is disadvantages because it tends to limit the drug development process those diseases for which good animal models. Thus western medicines have produced many good drugs for hypertension, because anti-hypertensive clinical activity can be predicted in animal models, as well as many good drugs for some infections because antibiotics can be screened. Compare approaches are not possible for diseases that good animal. As a result of these findings, the pharmaceutical industry has been less successful in development new drugs to treat such diseases, rheumatoid arthritis or chronic hepatitis, the Herbal remedy prescriptions of most interest to western medicine are those offer hopes for treating diseases for which good animal models do not exist and which therapy with western drugs may therefore remain inadequate. An important consequence, then, of reconciling the philosophical approaches of western medicine and Herbal remedy medicine might be to find satisfactory western way of evaluating Herbal remedy prescriptions claiming to treat diseases that may not be created adequately by drugs developed by western medicine.

Evaluating Herbal Remedy as Clinical Trials

The main component of such an evaluation will be a clinical trial that is designed to test the therapeutic efficacy of an Herbal remedy medicine. Recently discussed the problem of trying to evaluate a Herbal remedy prescription according to the Standards used by the Government in Each Country to evaluate western drugs. Criteria is an indispensable component of such an evaluation, but I indicate that it might be difficult for a crude Herbal remedy prescription to meet the Government in Each Country usual requirements for the chemical characterization of a potential new drug. Other problem, however, is one of equity; the question of whether to evaluate a Herbal remedy medicine by the procedures ordinarily used to evaluate a western drug. Thus, comparing a Herbal remedy medicine with a placebo in a randomized, double-blind study may be appropriate for the purpose of determining whether or not the drug qualifies for government approval. Herbal remedy prescriptions however were developed in the cause of years of experience in matching a patient's symptoms to an appropriate "SHO". Is it reasonable, to evaluate such a prescription by determining its effectiveness in a patient whose illness is diagnosed according to western guide line? Is it not more appropriate to attempt to evaluate Herbal remedy therapy with in the context of the therapeutic system that spawned its development?

Antioxidant assay is necessary to put into *in vivo* or *ex vivo* system-vin Blanc is not enough for?

The temporal disappearance in human blood plasma of

endogenous antioxidants in relation to the appearance of various classes of lipid hydro peroxides measured by HPLC post column chemiluminescence detection has been investigated under two types of oxidizing conditions. Exposure of plasma to aqueous peroxy radicals generated at a constant rate leads immediately to oxidation of endogenous ascorbate and sulfhydryl groups, followed by sequential depletion of bilirubin, urate, and alpha-tocopherol. Stimulating polymorph nuclear leukocytes in plasma initiates very rapid oxidation of ascorbate, followed by partial depletion of urate. Once ascorbate is consumed completely, micromolar concentrations of hydro peroxides of plasma phospholipids, triglycerides, and cholesterol esters appear simultaneously, even though sulfhydryl groups, bilirubin, urate, and alpha-tocopherol are still present at high concentrations. Non-esterified fatty acids, the only lipid class in plasma not transported in lipoproteins but bound to albumin, are preserved from per oxidative damage even after complete oxidation of ascorbate, most likely due to site-specific antioxidant protection by albumin-bound bilirubin and possibly by albumin itself. Thus, in plasma ascorbate and, in a site-specific manner, bilirubins appear to be much more effective in protecting lipids from per oxidative damage by aqueous oxidants than all the other endogenous antioxidants. Hydro peroxides of linoleic acid, phosphatidylcholine, and cholesterol added to plasma in the absence of added reducing substrates are degraded, in contrast to hydro peroxides of trilinolein and cholesterol linoleate. These findings indicate the presence of a selective peroxidase activity operative under physiological conditions. Our data suggest that in states of leukocyte activation and other types of acute or chronic oxidative stress such a simple regimen as controlled ascorbate supplementation could prove helpful in preventing formation of lipid hydroperoxides, some of which cannot be detoxified by endogenous plasma activities and thus might cause damage to critical targets. Extracellular release of superoxide anion and hydrogen peroxide during the respiratory burst of porcine neutrophils was studied by using diacetyldeuteroheme-substituted horseradish peroxidase as a trapping agent for these oxygen derivatives. The method permitted simultaneous measurement of oxygen consumption and formation of both O_2 and H_2O_2 in a single reaction mixture. When neutrophils were stimulated with phorbol myristate acetate in the presence of the home-substituted peroxidase, a rapid accumulation of compound, a complex of the enzyme with O_2 , was observed accompanying an increase in oxygen consumption. During the process, amounts of compound formed and oxygen consumed were stoichiometric, and no compound II, an indicator of H_2O_2 formation, was observed. These results establish that neutrophils stimulated with the phorbol ester produce exclusively O_2 as the primary oxygen metabolite and release it into the extracellular medium. When a limited amount of opsonized zymosan was used as the stimulus, compound formation was also observed but it ceased at an early stage of oxygen consumption. When a sufficient amount of azide was included in the system, however, formation of compound II was noted in the later stage of oxygen consumption. The findings suggest that O_2 , formed during phagocytosis, is converted to H_2O_2 within phagosomes and then diffuses out into the extracellular medium when its decomposition by catalase and peroxidases are blocked by chelating agent.

Conclusions

The conclusions were as following:

1. QOL have to be explained by digital words not by analog one.
2. Possible scale is immunological factor including complement. Simple sum-up and make mean fade out the constitutional change (Figure 2).

3. Constitutional change was explained by coefficient dependent factor (Figure 3).
4. Emotional Hormone also important scale for CAM assessment (Figure 4).
5. Complement system deeply concern with CAM, especially by fermented products.
6. Alternative Complement cascade might be break through Alternative Medicine.
7. Traditionally derived medicine, Cordesepin, dogged out for apoptosis and autophagy agents to many kind of human tumor cells.
8. Anti-oxidative assay should be made in at least *ex vivo* system, not in *in vitro*.
9. Vin Blanc showed the same anti-oxidative activity in *ex vivo* macrophage.

Conflict of Interests

No conflict of interest hit in this issue.

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