Thymus Extracts:
An International Literature Review of Clinical Studies*

reviewed by

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The past 20 years have witnessed an explosive investigation of the immune system and the agents governing it. One area of research involves the use of thymus extracts. These extracts have proven surprisingly useful in a wide variety of conditions, sometimes being the only effective treatment (Skotnicki 89, Kouttab 89, Hadden 89).

Overview

A brief explanation of cellular and humoral immunity.
Although immunity involves every orvm and system of the body, the typical conceptualization of the immune system consists of lymphocytes divided into two major divisions: the humoral mid cellular aspects. Humoral immunity includes primarily B lymphocytes and has to do with antigen/antibody reactions. These are the reactions involved in type I (immediate hypersensitivity, IgE response, anaphylaxis), type II (hemolytic disease of the newborn) also known as erthyroblatosis fetalis) and type III (Arthrus) hypersensitivities. In antigen/antibody reactions, B lymphocytes secrete antibodies to an antigen. An antigen is any substance, typically a protein that the body recognizes as "non-self". The antibodies attack an antigen by clumping around it. Simultaneously they weaken it and signal for other aspects of the immune system (especially the complement system and phagocytosis) to immobilize and dispose of the antigen. No direct contact of the B lymphocyte with the antigen is necessary. Cellular immunity, however, is mediated primarily by the T lymphocytes and involves cell to cell contact with microorganisms and other pathogens. The T helpers, T suppressors, T cytotoxic, killer (K) cells and natural killer (NK) cells are part of the system. Macrophages and monocytes are also recruited by members of this array of cells and are involved in constant direct combat with the pathogens and renegade cells that constitute most of the chronic diseases from which we suffer. The cellular branch of immunity is, therefore, responsible for vigilance against neoplastic and aging cells, as well as viruses, fungi (Odds 94), and some bacterial (Berkow 87, P260) and parasitic infections (Rothbard 90, Gasbarre82).

Maturation of T lymphocytes
Historically, T lymphocytes mature in the thymus gland but we a part of the myelopoietic cell line and have their origin in the bone marrow. As they develop, they carry specific cell surface markers on the periphery of each cell which we used to identify each cell type. These cell markers change as the cell mature. Immature thymocytes in bone marrow carry a CD1 (also known as T1) marker. Some of them migrate to the thymus gland for maturation beginning in the late part of gestation. The rest continue to migrate to the thymus throughout life with the greatest migration taking place in the first two years of life and at 13-16 years of age. As they mature and begin to migrate out of the bone marrow, thymocytes drop the CDI marker and begin carrying a CD3 lymphocyte cell surface marker. When a CD3 (also known as T3) cell is brought into contact with an antigen appropriate for a cdlulu immune response, the T cell nm=es by committmg to that particular antigen and becomes a T helper/inducer cell and hence adds a CD4 (also known as T4) marker to its cell surfiice. Other T cells become suppressor or cytotoxic cells wbich carry CD8 (also known as TS) markers. Once T cells an committed, they remain vigilant and committed to that antigen for life but depend upon the presence of the thymic hormones for normal activity (Berkow 87, P260-1). Thymic hormones and their down stream cell products (such as interleukins and interferons) control all phases of maturation, development antigen commitment, proliferation and cytotoxic activity of the various T cells. Thymic hormones also stimulate non-specific phagocytic and cytotoxic cells to respond against foreign or non-self antigens.

Causes of compromised immune function
It is hard to exist and not pose some insult to the immune system indeed. Indeed, it is the combination of what the body is exposed to and its ability to respond that comprises the adequacy of the immune response. In any epidemic, only a portion of those exposed become infected , only a portion of the infected become ill and only a portion of those who become ill are overcome and die. The difference in each of these stages is the adequacy of the response of the immune systm There are

many factors which have been shown to affect immunity. Nutrient status has been shown to be fundamental to a proper immune response (Berkow 92, P317). Inadequate nutrient intake results specifically in T cell immunodeficiency (Nezu 94, Wing 88); affects delayed-type hypersensitivity (DTH) skin tests; and reduces T cell numbers, proliferative responses to mitogens, and cytotoxic activity (Berkow 92, P3 18). In addition to overall nutritional status and sub optimal nutitional intake, the following conditions also lend the body to immunocompromised states: excess or lack of exercise (Wiik 96, Boyum 96); physical trauma (Wichmann 98), especially involving head injuries (Sacks 95, Meert 95, Quattrocchi 92) and burns (Cairns 94); inadequate amounts and quality of sleep (Born 97, Wiik 96, Boyum 96, Irwin 96); excess fatigue (Bennet 98); starvation (Nezu 94, Wing 88); smoking (McAllister 98); excessive intake of alcohol (Faunce 97); most recreational drugs including barbiturates (Nagylucskay 92). cocaine (Stanulis 97, Watson 83, Di Francesco 90), marijuana (Cabral 98, Klein 98, Tang 92. Specter 90); and prescription drugs such as steroids (Daynes 95, Berge 94) and narcotics (De Waal 98, Roy 96, Carr 95, Rouveix 92, Novick 91); introgenically induced stresses such as chemotherapy (Periti 97, Rosenthal 87, Rosenthal 88, ten Berge 94), surgery (Samanci 98, Brivio 98, Zaporozchenko 98), radiation (Lieber 98, Tisch 98, Krutmann 98) and some antibiotics (Fietta 83, High 92, Berge 94); extremes of weather (Komarov 85, Stott 76, Kohnlein 73); aging (Hadden 89, Weksler 81); and cbronic disease (Fiocchi 86, Cazzola 87, Tas 90). None of the clinical trials reviewed in the following text have attempted to control for more than one of these variables. These additional factors affecting overall immune status will critically influence the effectiveness of specific immuntherapy in restoring an adequate immune response.

Thymus Extracts

Composition of thymus extracts

There has been some confusion concerning the composition of thymus extraxts. In part this has arisen because different products contain varying amounts of three different active hormones isolated from the thymus: thymulin (also known as facteur thymique serique or FTS), thymopoietin and thymosin alpha 1. Two other partially purified active substances, thymsin (TP-1), also contain constituents of lymphocytes and epithelial cells in addition to one of the thymic hormones (Hadden 89). The shortest active thymus fraction producing demonstrable activity is an oligopeptide (fraction V) with a molecular weight of 3108 Daltons (Badamochian 97). Other confusions have arisen due to misleading literature from some companies claiming that their products are hormone free. Commercial preparations, whether liquid or solid, have typically contained at least one of the three thymic hormones because eliminating all of the thymic hormones and other active fractions from the stroma and parenchyma of thymus tissue is a difficult procedure. To the author's knowledge, none of the commercial preparations claiming to have eliminated the hormone fractions filter out these low weight molecules as it is costly procedure requiring special filter and equipment and is difficult to achieve on a commercial scale. Purification of one or more of the fractions, however, has been done successfully on a commercial basis for a number of years. Most of the commercially available thymus fractions are presently derived from bovine thymus, except for thymulin which is derived from porcine serum (Hadden 89). Virtually all of the literature appearing in peer reviewed journals involvmg the use of thymus extracts have used liquid varieties. No studies using powdered thymus extracts were seen in reviewing papers published in the last 25 years.

Biological properties of liquid thymus extracts

Although there is some evidence for improvement in B lymphocyte function (Twomey 82), most of the improvements seen using thymus extracts have been within the cellular branch of immunity involving T lymphocytes (helper/inducer, suppressor, cytotoxic, NK cells, K cells and macrophages). Thymus extracts have been shown to modulate the production, maturation and activation of T lymphocytes (Skotmicki 89, Kouttab 89, Hadden 89) and macrophages (Andolina 87) and to stimulate conversion of immature thymocytes (T6 cells) to non-dedicated T cells (T3 cells) in human bone marrow (Kouttab 89). In the more mature T cells, thymic extracts have been shown to effectively increase the number and function of T helper/inducer lymphocytes (T4 cells) (Stankiewiez 86) and of suppressor cells (T8 cells) (Kouttab 89). Thymic extracts have also been shown to enhance responsiveness to concanavalin A (Con A) (Dabroski 80)and phytohemagglutinin (PHA) (Segatto 86), even in patients with gastrointestinal tract maligancies (Park 84) or in cells treated with cyclophosphamide (Poli 86), a strong immunosuppressor. These are important findings as both PHA and Con A are major in vitro tests for T cell mitogenesis (proliferation) and increased cytotoxic activity in T cytotoxic cells (Rosen 89). Lymphocytes in patients with malignancies and those treated with drugs such as cyclophosphamide are typically unresponsive to PHA or Con A. Thus, thymus extracts have been able to produce an immune response in laboratoxy tests, even in significantly immunocompromised patients who were previously unresponsive (Cangemi 93, Fagiolo 93). In addition to labratory tests for immune competence, clinical tests for cellular immunity are sometimes employed. The most common is the delayed-type hypersensitivity (DTH) skin test. Small amounts of test antigens such as candida, streptokinase/streptodornase (Sk/Sd), tetanus toxoid (Berkow 92, P308), mumps, and trichophyton antigens (Berkow 87, P279) we injected subdermally. These antigens normally produce a raised and indurated skin wheal several millimeters in diameter, 24-48 hours after injection. A lack of reaction to this group of antigens indicates a lack of immunocompetence of the cellular immune response. Thymus

extracts have been shown to regenerate and/or increase the production and activity of T lymphocytes and macrophages and/or to effectively restore skin test responsiveness in previously unresponsive patients (Lasisz 90, Periti 93). Extracts of thymus glands from bovine, ovine or porcine sources have been available for more than 65 years (Harrower 32). Most of the basic and clinical research has been conducted over the past 15 years in Russia, Poland, Italy, Spain, Germany and Switzerland. There are several different liquid thymus products appearing in the literature. Overall, the results using these liquid preparations are encouraging, demonstrating an effectiveness of thymic fractions whether adminstered by injection or taken orally (Kouttab 89).

Clinical Applications of Thymus Extracts

As mentioned above, the cellular branch of immunity is responsible for vigilance against chronic viruses, fungi, yeast, and parasitic infections as well as neoplasms and aging. Thymus extmcts have been used clinically in a variety of ways involving some of these conditions. They have been used orally and as injectables; by themselves and in combination with other therapeutics. Thymus extracts have been used to treat severe and chronic allergies involving the respiratory tract and skin as well as in severe acute and chronic infectious diseases. The extracts have also been shown to reduce post surgical infections, decrease the damage of chemotherapy and radiation and have been used as adjuncts to mainstream therapy for treatment of neoplasms. The review of literature presented below is a survey of the conditions treated using thymus extracts and demonstrates the research completed to date using thymus extracts.

Infections

The effector mechanisms involved in the immune response against infectious agents are mainly macrophages, natural killer (NK) cells, granulocytes, and T and B lymphocytes (Kouttab 89). Clinical improvement depends heavily upon the number and competence of these cells. Hence, cellular immunity is a key to proper recovery from infective states.

Respiratory Ailments

Recurrent respiratory infections (RRI) in chil dren

Double blind studies revealed the thymomodulin, a thymus extract, given orally to children was able to reduce the number of RRIs compared to placebo controls and to previous year infections in the same child. An increase in CD3 and CD4 cells, neutrophil functions and salivary IgA levels was also seen (Fiocchi 86). The same extract was also successfully used with RRI. Continued use prevented relapses of infections and produced an increase in phagocytic responses of aleveolar macrophages and serum immunoglobulins (Kouttab 89). Another calf thymus extract, TFX was compared to levamisole (Ergamisol), a pharmaceutical immunomodular, in a placebo controlled trial to treat children suffering from chronic bronchitis. The children chosen for the study had a minimum of 9 months of recurring bronchitis with at least 1 episode per 2 months and were from 19 months to 10 years of age. Both of the treatment groups (TFX and levamisole) showed statistically significant decreases in the number, severity and duration of episodes, and each group required less antibiotic therapy. There was also a tendency toward normalization of the number and function of T lymphocytes in both groups (Skotnicki 89, Radomska 87).

Adult bronchitis

Improvement was also seen in 20 of 26 adults with recurrent upper respiratory tract infections (URI). All subjects were experiencing 8 to 10 severe episodes/year and were resistant to antibiotics, vaccinations, inhalations and other treatments. Each received the thymus extract, TFX, orally daily fbr 1 month and every second day thereafter for 12 months. Quantitative and/or functional improvements in T lymphocytes were seen in 70% of the patients. These improvements corresponded with clinical improvement manifested by decreased number and severity of episodes, and decreased or no need for antibiotics. One year after treatment was discontinued, patients still reported an improved status. The physician's conclusion was that thymus extract was "the treatment of choice" as it effectively changed the natural course of the disease by working at the causative level; ie. the faulty immune process, rather than at the combative (antibiotics) or symptomatic (bronchodilators, etc.) levels (Stankiewiez 86).

Chronic spastic bronchitis

Treatment with TFX thymic extract infections 2x/week for one year used in conjunction with Encortolone [prednisolone (Arizona 93)] (4-12 mgtday) produced clinical improvement and normalization of the granulocyte phagocytic index, but did not alter the defective response in granulocyte migration tests (MIF) (Matusiewicz 87). The author attributed the lack of change to the immunosuppressive effect of the steroid. Similar results were found in other studies (Gieldanowski 81, Smogorzewska 84) confirming that thymus extracts can yield a greater clinical benefit in pulmonary infections

than steroids by themselves. Although response is greater and complications fewer, lasting improvement should not be expected when used in conjunction with immunosuppressive steroids.

Bronchial asthma in patients with atopic dermatitis
One-hundred and sixty-three patients treated for bronchial asthma with the thymus extract, vilozen, showed improvemnt in clinical signs and symptoms as well as T cell activity. The substance was said by the author to correct the immune disorder (Kogosava 90). Orally administered thymomodulin improved clinical symtoms and reduced the frequency of acute allergic episodes as well as decreased IgE titers and eosinophil counts (Kouttab 89, Fiocchi 97) in subjects suffering from combined bronchial asthma and atopic dermatitis (Bagnato 89). Thymus extracts have also been used with patients suffering from combined bronchial asthma and atopic dermatitis to help counterbalance the unfavorable environmental effects of living in polluted air caused by a large industrial power plant. The treatment helped raise immune responsiveness of these patients and significantly increased treatment efficacy of bronchial dilators (Grigor'ev 89).

Chronic Respiratory Infections

Angina & bronchitis
Eighty-six patients with angina and concomitant bronchitis received antibiotics, splenin (a spleen extract) and vilozen (a thymus extract) in a clinical trial. They were compared to 52 controls who received routine treatment. [Routine treatment for angina is typically nitroglycerin under the tongue upon attack. Treatment for bronchitis is rest, fluids and antipyretic and/or analgesic drugs (Berkow 92, P504 & 658 respectively)]. The results revealed that a combination of splenin and vilozen produced a pronounced fortification of the immune response in the treated group, consequently improving their clinical status. The authors recommend that immuno-modulators (thymus and spleen extracts) are indicated in the treatment of repeat and relapsing angina, especially in the presence of concomitant bronchitis (Frolov 92).

Chronic obstructive pulmonary disease (COPD)
COPD is the combination of chronic obstructive bronchitis and emphysmna (Berkow 92. P358). The imbalance of phagocyte functions in COPD include a reduction in PMNs (polymorphonuclear leukocytes) and monocyte chemotaxis and a decreased killing capacity due primarily as a reduced myloperoxide capacity of these cells. A prospective randomized trial was completed on 78 patients with COPD. Thirty-eight patients were given the thymus extract, thymostitmulin (TP-1), intramuscularly (l mg/kg/day) for the first week followed by once per week for 6 months, in addition to the standard treatment for COPD. Patients receiving thymostimulin showed statistically significant fewer exacerbations and hospital visits during the one year follow-up period compared to the 40 controls receiving standard treatment only. However, there was no change in the number of patients with severe or moderate impairment of respiratory function. Also, there were no changes in serum immunoglobulin or T cell subsets (Banos 97). In another study, patients suffering from COPD were given thymostimulin (TP-1) for one year and assessed during and after the trial period. The results showed a return to normal of myloperoxide capacity. Phagocyte functional capacities, however, were unaffected. A significant improvement of clinical status was also seen during the one-year program. Because of the laboratory and clinical improvement seen, the authors suggest that thymo-stimulin be considered in the treatment of COPD (Tortorelia 92).

Diseases and Infections of Viral Origin

Tuberculosis
Thirty older patients with active tuberculosis were given the thymus extract t-activin (tactivin) as part of a multimodal therapeutic regimen. The results showed an elevation of T helper cells, enhancement of lymphocyte activity and increased IL-2 synthesis. Enhancement of natural killer cell activity and IL-1 synthesis by macrophages were also observed. This normalization of specific and nonspecific immune responsiveness paraleled clinical improvement. (Adambekov 98).
The same thymus extract appeared to benefit a group of patients suffering from pulmonary tuberculosis and type I diabetes mellitus combined. Overall, patients with these combined illnesses indirectly showed more depression of cellular immunity, as indicated by a decrease in the number of T- lymphocytes and decreased blast-cell transformation, than those with tuberculosis alone. When t-activin was added to the drug therapy regime, immune parameters normalized. The author also noted a more rapid recovery and more frequent incidence of recovery from tuberculosis in the treated group. They suggested t-activin be added to the therapeutic regimen of patients suffering from type I diabetes and tuberculosis. The authors also noted a more frequent and rapid recovery from tubercuulosis in the treated group. As a result of the study, they suggested considering the addition of immunomdulators such as t-activin as part of the therapeutic regimen in type I diabetic patients with tuberculosis (Karachunsiki 97).

Herpes simplex (RSV)
Herpes simplex is a virus belonging to the herpesvirus group. Herpes simplex type I (herpes labialis, cold sores or fever blisters) is transmitted primarily via oral or respiratory routes. Herpes simplex type 2 (henm genitalia) is transmitted primarily by sexual contact (Tortora 86, P536-7). The virus remains dormant in the skin or nerve ganglia until triggered by over exposure to sunlight, physical or emotional stress, or certain foods or drugs (Bm-kow 87). if immunity is not established early in the course of the disease, infection is usually lifelong. The thymus extract, TFX, was used to successfully treat 8 patients suffering from recurrent herpes simplex labialis. Patients received the extract every second day for the first month, then twice weekly for 12 months. No reoccurrences were seen during the 12 months in 3 patients who had previously averaged 5 to 10 outbreaks per year. Clinical improvement was noted in 5 others. Frequency, duration and severity of reoccurrence were all substantially reduced while taking the extract. Cessation of the treatment, however, was associated with a return to the previous characteristics of the illness (Skotnicki 89).

Herpes zoster
Herpes zoster is another herpes-type virus that causes chicken pox and shingles (Tortora 86, P534). Although usually a self-limiting viral disease, herpes zoster was used as a clinical model to study the effects of thymus extracts in 28 otherwise nonimmunocompromised patients. Results of this double blind study reported an accelerated rate of wound healing, shorter duration of vesicles, shorter time to first and crusting lesions, as well as a greater amelioration of pain during the acute phase (Skotmcia 89). Thus, thymic extracts were shown to be effective in treating viral infections in nonimmunocompromised subjects. This was further underscored in a study treating 5 cases of recurrent humna papilloma virus (HPV) where each patient received thymostimulin therapy IM for 9 months. The results showed a reduction in size and number of lesions (Grismondi 91). Note that this is a disease not thought to result from a deficient immune fimction, yet treatment with thymus extract was beneficial.

Acute and chronic hepatitis B
Hepatitis B is caused by the hepatitis B virus (HBV) and is associated with a wide spectrum of liver diseases, including a subclinical carrier state, acute hepatitis, chronic hepatitis, cirrhosis and hapatocellular carcinoma. Chronic Hepatitis B occurs in 5-10% of patients who initially contacted acute hepatitis B infections (Berkow 92, P902).

Acute hepatitis B: Significant decreases were seen in total bilirubin and iron levels in conjunction with more rapid clinical improvement and shorter hospitalization time in a group of 15 patients with laboratory comfirmed acute hepatitis. Patients were given 15 injections of the thymus extract, TFX, beginning the day of diagnosis and followed over the course of the disease until recovery (Kicka 86).

Chronic hepatitis B: Chronic hepatitis B is a difficult disease to treat and has a varying prognosis. Only about 1/3 of the cases develop from acute hepatitis. Most develop insidiously de novo (Berkow 92, P905). The disease has varying courses. "Mild persistent hepatitis, full blown chronic active hepatitis with eventual cirrhosis, and a subclinical chronic carrier state all occur. The latter is especially prone to lead ultimately to hepatocellular carcinoma." (Berkow 92, P903). Illnesses associated with HBV tend to progress and are usually relatively resistant to therapy (Berkow 92, P906). With present medical therapy, patients usually live several years, but hepatocellular failure, cirrhosis, or both eventually develop in many cases (Berkow 92, P906). The liver injury in HBV is due to an immune mediated host reaction to the infection and not the infection per se (Berkow 92, P905). The use of thymus extracts to normalize the aberrant immune responses seen in hepatitis B is a logical treatment choice. Consistent with this line of reasoning, 18 patients with biopsy proven chronic active hepatitis B and a lowered T4/T8 ratio received thymic extract TFX for 6 and 12 months in two different groups (Dworniak 91). Improvement in the T4/T8 ratio was seen beginning 14 days after treatment had begun, followed by a decrease in the abnormally high NK cell count. As the NK cell count decreased, NK cell migration and killing activity increased to normal in both the 6 and 12 month groups. Normalization of biochemical and immunological parameters occurred within 5-6 months of beginning treatment. Seroconversion of HBe system to anti-HBe was observed after 9-12 months in both of the treatment groups. HBe is a blood marker for presence of the virus core. lt indicates active viral replication. Seroconversion to anti-HBe (the antibody to HBe) indicates the viris has ceased replication. This seroconversion usually portends a benign outcome (Berkow 92, P906). A two year follow up showed continued clinical remission with normal immunological and biochemical panels in both groups. The authors conclude that the thymus extract had an immunostimulatory action of lasting duration. A similar study using TFX fbr 6 months on 29 patients produced similar findings with similar conclusions (Zeman 91). In another study, thymomodulin thymus extract was administered orally as a syrup at a dose of 120 mg/day fbr 1 year to a group of children with chronic hepatitis B who had a positive HBs Ag and HBe Ag blood profile. The results showed a higher rate of recovery and seroconversion to anti HBe than controls (Bortolotti 88, Raymond 98).

Other liver diseases including **chronic cholestatic hepatitis and primary biliary cirrhosis** have been successfully treated by the thymus extract, t-activin. Results of a study using 102 patients with chronic cholestatic hepatitis primary biliary

cirrhosis showed an increase in T lymphocytes, increased functional activity of mononuclear cells (increased chemotaxis and inhibition), and decreased immunoglobulin counts. All of these indicators signify an increased immune competence which favors controlling the immunoinflammatory process in the liver and a normalization of the clinical manifestation of the disease leading to a favorable outcome (Radchenko 92). These new results are important not only for the successful treatment of a very difficult disease which frequently has an unfavorable outcome, but also for the implications for treatment of hepatitis produced by other causes. Many of the inflammatory conditions of the liver are caused by viruses, fungi, or mycobacteria (tuberculosis) (Berkow 92, P898). Cellular immunity is the chief defense against these agents. Successful treatment of the above conditions using thymus extracts suggests many exciting possibilities for treatment of presently untreatable ailments of the liver using immunomodulating substances such as thymus extracts.

Recurrent aphthous stomatitis (RAS)
In a small clinical trial, 5 patients suffering from recurrent aphthous stomatitis for periods ranging from 2 to 8 years entered a 2 year trials using the thymus extract, TFX. An overall beneficial effect was seen in 4 out of 5 patients as shown by decreased pain frequency and duration of lesions in 2 patients and a complete disappearance of lesions in 2 others. Discontinuance of treatment, however, brought about the return to the pretreatment condition for all patients within 12 months after cessation (Skotnicki 84). As no drugs are known to be effective in treating RAS, its successful treatment using thymus extracts should be considered a therapeutic breakthrough. Even though the results were not long lasting, the therapeutic regimen was effective as long as treatment was continued.

Dysentery due to Shigella infection
Chronic and lingering dysentery due to Shigella infection was successfully treated in 51 patients using the thymus extract, t-activin (Guliamov 91). In their discussion, the authors emphasized that the cause of chronic dysentery was a fractional defect in the lymphoid and phagocytic cells of the colonic mucosa with an analogous defbct in the peripheral leukwytes. The administration of thymus extract not only eradicated the pathogenic organisms, it also connected the functioual defects in the lymphoid and pbagocytic cells. reduced inflammation and ameliorated repair of the inWMW mucosa.

Acute Inflamation of the maxillofacial areas
One study reported improvement in hypo/hyper-inflammatory reaction using local subcutaneous and endolymphatic injections of t-activin with patients suffering from acute inflammation of the maxillofacial area. Overall improvement of patient saw and an arrest of inflammatory processes was reported using this technique (Drobyshev 96). Another study using T-activin with 46 patients affected with acute inflammatory disease of the maxillofacial area also showed improvement of depressed immune function (Bazhanov 96).

Immunodeficiency Diseases

Combined Immunodeficiency This is a group of disorders characterized by congenital and often hereditary deficiency of both B and T cell systems, lymphoid aplasia, and tbymic dysplasia. This is a disease typically manifesting within the first three months of age with pneumonia, thrush and diarrhea. Treatment is usually with immunoglobulinx and antibiotics initially, followed by bone marrow mtransplant. The untreated course is usually fatal before the age of two (Berkow 92, P315). Using the thymus extract, TP-1, some improvement was seen in 4 children with this disease (Davies 82). Total reconstitution of immunity was not achieved and multiple drug regimens were needed to sustain life in these children with 1 child succumbing to complications of bone grafting. Two of the 4 children, however, did show marked improvement of immune function. Monthly injections were needed to sustain the children as a decline in immunity was seen if the thymus extract was withdrawn.

AIDS
The most extreme example of viral infection of lymphocytes with resultant immunosuppression is acquired immunodeficiency disease (AIDS). The HIV virus is a retrovirus which causes the destruction of T helper/inducer (T4, CD4) cells. Several studies using various liquid thymus extracts have appeared with mixed results in peer reviewed journals. Although the lack of good experimental design and protocol makes these studies difficult to evaluate, some important findings have emerged. In one of the best designed studies, 15 ARC and AIDS patients were treated with liquid thymus extract orally (Valesini 87). The results showed significant increases in T cells, T helpers and in T4/T8 ratios. These indices play an important role in the pathogenesis of AIDS (Berkesi 85). Clinically, the number of patients demonstrating chronic lymphadenopathy decreased by 2/3rds, fevers disappeared in all subjects and the incidence of thrush decreased remarkably during and after treatment. One patient in the study had been diagnosed with Kaposi's sarcoma (KS). This patient was in complete remission when the study was submitted for publication, several months after treatment had ended. None of the patients with ARC progressed to AIDS during the study. These results helped to confirm those of an earlier study in which 3 subjects [one with AIDS and two with lymphadenopathy syndrome (LAS)] were responsive to

treatment with the same thymic extract (Valesini 86). In another study involving 34 subjects with ARC who received injections of a thymus extract 2 times weekly for 6 months, significant increases in leukocyte and lymphocyte counts, as well as a significant difference between control and treatment group T4 counts were seen after 12 months (Pailisano 88). Delayed-type hyper-sensitivity (DTH) skin tests, the standard clinical tests for competence of cellular immunity, also improved significantly along with the amelioration of other clinical indices such as weight loss, fever, night sweats and lymphadenopathy. Eighteen months after the treatment had begun, none of the 34 in the treatment group had progressed to developing AIDS, whereas 3 of the 24 in the control group had developed the disease. A similar study had similar findings including the difference between groups in their progression from ARC to AIDS (Carco 84). Twelve patients in the early stages of HIV infection were treated with the thymus extract, thymomodulin, 60 mg orally/day for 50 days. A normalization of the T4/T8 ratios with an increase in T4 cell numbers was reported along with improvement in the clinical course of the disease (Valesini 87).

Other researchers, however, found no difference in the clinical course of the disease or survival time using injections of the thymus extract, thymostimulin (TP-1) at l mg/kg per day for 14 days, followed by weekly injections for 12 weeks (Chachoua 89, Beall 90). The difference in outcome may have been an effect of the stage of the disease at which therapy was instigated, since both of the authors reporting no difference in the clinical outcome used subjects with more advanced cases. As AIDS cases advance, the T helper cells become severely decreased (Berkow 92, P83). One of the prime targets of thymic extracts appears to be the T helper cell. Decreased cell populations would, therefore, be consistent with decreased responsiveness.

The overall implication of these studies is that thymus extracts may be effective in stabilizing or sometimes reversing labratory and clinical manifestions of ARC and AEDS. The activity appears to be focused directly on the T cell lineage from pre T lymphocytes to mature T cells (Weksler 81). Although there were some concerns that this might indeed provide more T cells to be infected, no study has supported this.

Allergies

Perennial allergic rhinitis, bronchial asthma and atopic dermatitis are all known to result primarily from a defect in cellular immunity. All have shown benefit from using oral administration of thymus extracts (Kouttab 89, Genova 86, Fiocchi 87). In one study, 18 patients with chronic purulent rhinosinusitis were treated with TP-1 thymus extract administered daily by intramuscular injection for 14 days followed by 2 injections/week for 6 weeks further. All patients had demonstrable defects in their cell-mediated immune system before treatment had begun. All 18 patients showed clinical improvement. Twelve out of 15 reported feeling better during TP-1 therapy. Thirteen patients showed an absence of mucopurulent secretion in the nasal mucosa. Positive bacterial culture rates from nasal mucosa decreased by 2/3rds from 14 out of 15 subjects to 5 of 15. The clinical improvements were accompanied by an increased performance of functions of the cell-mediated immune system the most significant of which was increased monocyte activity (Tas 90). Placebo treatment had no significant effect.

Skin Diseases

Atopic eczema

Beneficial results using thymus extracts have also been obtained with children suffering from atopic dermatitis (also known as atopic eczema and AD). One characteristic of this disease is a nightly occurrence of intractable itching which causes uncontrollable scratching of lesions. The itch-scratch-irritated rash cycle due to the circadian elevation of IgE and consequent mast cell release of histamine at the lesion sites is a significant part of the symptom picture. Poor wound healing and consequent infection and reinfection from scratching disrupted lesions is common. Atopic children and adults also frequently suffer from food allergies caused by the hyper IgE response patterns. The source of this disease is thought to be a defect in T cells via indirect regulation of IgE responses (Berkow 92). This is a problem seen daily in dermatology clinics and is associated with other immune defects such as hay fever, rhinitis and bronchial asthma.

Twenty atopic children were given the thymus extract, thymodulin, 3mg/kg/day for 30 days. A disappearance of the circadian variability of serum IgE and hence the of nightly itch-scratch cycle was seen in the children under treatment, whereas no improvement was seen in controls (Pecora 91). A clinical trial using the elimination provocation dietary regimen was insti tuted with 20 atopic children, 10 of which received the thymus extract, Thymodulin, during the elimination phase and 9 of which were only withdrawn from food they had previously shown sensitivity to. After 90 days the offending foods were reintroduced, skin lesions worsened and IgE levels actually increased in controls but no increase was seen in either the skin lesions or IgE levels (specific or nonspecific) in the groups receiving the thymus extract. IgE levels actually decreased during the treatment phase for the groups receiving thymus extract. The authors concluded that thymus extract was useful in modulating IgE disregulation in atopic children (Cavagni 89). Other studies have shown a general improvement in the

overall condition of atopic children receiving thymus extracts (Kouttab 89, Katiuzhnaia 90). Only one study failed to find any significant changes in either clinical or laboratory results (Harper 91).

Psoriasis
Psoriasis is a disease affecting 24% of the white population. Lesions vary from 1-2 lesions to widespread dermatosis: from disabling arthritis or exfoliation to guttate-rash in the throat (Berkow 92, P2435). Treatment varies from topical applications of substances such as coal tar and creams to systemic use of corticoid steroids or even the cancer drug, Methotrexate (Berkow 92, P2435). A group of 74 patients with varying severity of psoriasis (46% were classified as severe) was treated with TFX injections 3x/week for one month followed by twice weekly injections for 1-2 years. Results showed that 76.4% of the participants had remission of their lesions. Of the patients suffering from severe psoriasis, 33% showed an excellent response and 36% showed a good response. Ten of the 74 cases had long lasting remission after discontinuing the drug for more than 2 years. During the treatment period, a decreased sensitivity to viral and bacterial infections and an improvement in general clinical state and well-being was also reported (Skotnicki 89).

Autoimmune Diseases

Rheumatoid arthritis
Rheumatoid arthritis is a crippling and debilitating joint disease affecting approximately 1 % of the North American population. Its etiology is suspected to involve autoimmune mechanisms (Berkow 92, P1305). Several studies have shown the effectiveness of thymus extracts in treating this disease. TFX thymus extract was used in a trial in which 20 subjects received daily injections for 3 months. Eighty percent of those involved showed clinical improvement as evidenced by decreased joint swelling and tenderness and an increase in muscle strength. Forty percent showed a decrease in rheumatoid factor alpha 2 and serum IgG levels as well as an increase in hemoglobin and serum iron levels (Skotnicki 86). Similar results were obtained in two other studies (Skotnicki 89, Lasisz 90). It was concluded in these papers that TFX was of therapeutic value in the management of RA patients either alone or in combination with anti-inflammatory or basic anti-rheumatic drugs. A separate review paper supported these findings (Skotnicki 84). In another study, monotherapy with methotrexate (MT) was compared to combined therapy with MT plus t-activin thymus extract in a 2 year clinical trial involving 127 patients with RA. MT was given to 88 patients in a weekly dose of 7.5 mg. In 39 patients this dose was given in combination with injections of t-activin (100 mcg) twice a week for the first month and once a week for the remaining 2 years. In both groups there was **a** significant reduction in severity of arthalagia, number of joints with inflammation, severity of pain, C-reactive protein levels and erythrocyte sedimentation rate (ESR). In the combined therapy group there was also a reduction in morning stiffness and joint pain on palpation. The addition of t-activin did not significantly change the side effects of Methotrexate (Oliunin 96).

Systemic lupus erythematosus (SLE)
The efficacy of the thymus extract, t-activin, on cellular immune status of 49 children ages 8-15 suffering from SLE was examined. Treatment with t-activin for 4 weeks resulted in overall improved health and a reduction of SLE activity. A rise in serum thymic factor and increased T lymphocyte differentiation was also seen. In patients with secondary infections, an increase in absolute lymphocyte count, increased phagocytosis, and **a** rise of serum bactericidal activity resulted in the elimination and prevention of the development of secondary complications of infections. The author's conclusion was that t-activin promoted the normalization of the thymic structure and exerted a thymic hormonal replacement effect not seen in the control group of 34 SLE children who received no thymus extract (Karatasheva 91). Another author used t-activin to treat SLE in 17 adult patients. The results showed **a** regression of the articular and cutaneous syndromes as well as a regression of trophic disorders. The improvement was attributed to the functional enhancement of the neutrophils. Further tests showed an increased ability to phagocytize killed
Staphylococcus in vitro (Romanov 92).

Scleroderma
Even difficult diseases such as scleroderma showed response to thymus extracts used alone (Skotnicki 89, Suchkova 90) or in conjunction with other drugs (Suchkova 90). The results of both methods showed a decrease in the duration, severity and dissemination of the disease. This was correlated with a down regulation of the intracellular cAMP/cGMP ratio demonstrating an association between **a** functional defect in the lymphocyte regulatory mechanism and the disease (Suchkova 90).

Chronic autoimmune hemolytic anemia (AIHA)
In an unusual study of 8 patients with warm autoimmune hemolytic anemia (AIHA), TFX thymic extract was used after the patients had become refractory to treatment with glucocorticosteroids, azathioprine and splenectomies. Treatment with TFX resulted in 2 patients with nondetectable levels of antiglobulin. Five patients showed decreased levels of antiglobulin on the

test, direct antiglobulin [DAT, aka Coombs test (Jacobs, P602)]. In addition, eluate antibody and serum antibody levels were also decreased as were red blood cell autoantibodies. No adverse effects of TFX were noted (Slomkowski 96).

The above studies on autoimmunity, taken as a whole, present the interesting possibility that at least some thymus extracts may be able to help elevate and possibly normalize suppressor cell function.

Neoplasms

Cancer is typically treated with chemotherapy, radiotherapy and/or surgery. One difficulty with these treatments is that all three significantly decrease the ability of the system to adequately function. Yet an adequately functioning immune system is essential for any sustained recovery. Impaired cell-mediated immunity, in particular, is involved not only in the growth but also in the spread of cancer (Berkow 92, P1288). The following is a summary of various cancers and their treatment regimens involving the use of thymus extracts. In some studies, thymus extracts were used as the only therapy. However, more frequently, the thymus extracts were used as an adjunct to conventional therapy in an effort to help restore the immune system or prevent its profound depression and the immune related complications typically associated with conventional treatment. In most instances, thymus extracts helped restore immune function or decreased impairment and, in some cases, appeared to prolong the life of the patients. When reviewing the following studies involving neoplasms, it should be remembered that new therapies are typically tried on the most advanced cases with the poorest prognoses. Any alteration in the course of the disease produced by an experimental therapy is considered to be a significant event.

Lung Cancer

Cigarette smoking is associated with over 90% of all lung tumors. Lung cancers account for 35% of all cancers in men and 30% in women (Berkow 92, P'73 1). Survival time for over 90% of these patients is less than 8 months after diagnosis (Berkow 92, P731). Thymus extracts have been used singly and in conjunction with other therapies in an attempt to stem the rapid progress of these cancers and to modulate the deleterious effects of radiotherapy, chemotherapy and surgery. In addition to suppressing immunity, chemotherapy also produces alterations in the terminal airways even in an unaffected lung, i.e. chemotherapy causes a significant impairment of the alveolo-capillary barrier (the interface between the lung alveoli and capillaries). Radiotherapy reduces the total lymphocyte count and T cell CD4/CD8 ratio in the lungs. The concomitance of both therapies produces synergistic effects (Capelli 92) so that the use of chemotherapy in conjunction with radiation produces impairment of the alveolo-capillary barrier, which compromises oxygen exchange while simultaneously reducing the total lymphocyte count. Hence, there is a reduction of B, T and natural killer cells along with a reduction in cytotoxic and suppressor cells; the major defenses against cancer cells. Therefore, if competence in cell-mediated immunity and the related host survival rate is to be increased, immunotherapy is necessary just to overcome the adverse effects of the anti-cancer therapy given. This is in addition to re-establishing the already weakened immune competence evidenced by the presence of the cancer.

In One study, TFX used alone was administered twice weekly for 10 weeks to 12 patients suffering from either undifferentiated cell carcinoma or squamous cell carcinoma. Subjective and objective clinical improvements were seen in 10 of the 12 patients. An inhibition of local tumor growth and decreased metastatic spread to mediastinal lymph nodes or other organs was seen. Three Patients experienced a partial regression of tumor mass. The 6 month survival rate was increased to 42% in the treated group compared to 7% in the control group receiving only symptomatic treatment (Skotnicki 89). The effects of thymostimulin (TP-1) on chemotherapy induced toxicity and long-term survival were tested in 26 patients suffering from small cell lung cancer. Patients were randomly treated with 6 cycles of alternating chemotherapy regimens: cyclophosphamide, 4'-epidoxorubicin, and etoposide , alternated with etoposide and cysplatin. Fifteen of these patients also received TP-1 (1 mg/kg IM) on days 7-14 of each 3-4 week treatment cycle. At the end of the 6 cycles of chemotherapy, TP-1 (I mg/kg IM) was given twice weekly to complete responders until tumor relapse. Results showed that there were 7 complete remissions in the group receiving TP-1 as compared to 1 remission in the control group. Tumor progression was noted in 4 of the TP-1 group and 7 of the controls. Mean survival was 14.5 months for the TP-1 treated group and 5.5 months for the control group. The severity of neutropenia was significantly lower in the thymostimulin treated group, however duration of neutopenia was no different. There were significantly fewer chemotherapy induced side effects in the group receiving TP-1, especially in the severity and duration of myelosuppression as well as febrile and infectious episodes. The authors reported that treatment with TP-1 resulted in a better quality of life for patients and an improved ability to handle chemotherapy at increased doses and frequency
(Macchiarini 89).

Cohen et al. administered thymosin fraction V in conjunction with other chemotherapy (including Cyclophosphamide, Methotrexate and Lomustine) to patients suffering from small cell lung cancer for 6 weeks. This was followed by a regimen of the same chemotherapy in addition to a varying combination of vincristine sulfate, doxorabicin hydochloride and

procarbazine hydochloride, and epipodophyllotoxin, ethylidine glycopyranose (VP-16-213) and ifosfamide for a period of up to 2 years. The group receiving 60 mg/sqn body area of thymosin fraction V showed significantly increased survival time (434 days) compared to controls (263 days). After 1 year of treatment, 33% of patients receiving thymosin were disease free compared to 9% for controls. The authors reported some local skin irritation as a mild localized toxic effect of thymosin which subsided after 12 to 72 hours (Cohen 79). The synthetic thymus extract, thymosin-alpha 1, was used in conjunction with radiotherapy with non-small cell lung cancer patients in a randomized double blind study to determine whether it could reduce the immune suppression typically seen in radiotherapy. Following radiotherapy, one group (n=15) received twice weekly injections of thymosin-alpha 1I (900 mcg/lm2). The second treatment group (n=13) received a daily loading dose of thymosin-alpha 1 (900 mcg/m2) for 14 days followed by injections twice weekly as a maintenance dose thereafter. A third group received placebo injections on a similar schedule. Patients treated with thymosin using the loading dose schedule exhibited a normalization of T cell function by week 11, whereas patients receiving the twice weekly schedule exhibited only a partial T cell restoration which was not sustained over the 15 weeks of the study. However, the twice weekly schedule prevented the gradual decrease in the percentage of T helper cells seen in both the placebo and loading dose groups. Overall, the thymosin-alpha 1 treatment was associated with significantly reduced relapses and improved survival time which was most pronounced in patients with nonbulky tumors (Scholof 85).

Thymus extracts have also been shown to significantly reduce the immunosuppressive effects of radiotherapy in treating bronchogenic lung cancer even when the pretreatment immune responses of the patients are low (Vuckovic 92). Radiotherapeutically induced aggravation of initial immunodeficiency was prevented by giving the thymic preparation, Thymex L, to 10 lung cancer patients simultaneously with irradiation. A significant decrease of B and T cell numbers and decreased lymphocyte proliferative response to PHA were found in all patients before radiotherapy. Immediately after irradiation, proliferation responses dropped even lower compared to the pretherapy values. In patients treated with Thymex L, however, recovery from radiotherapy produced a significantly greater number of B and T cells and greater PHA-induced proliferative responses than those treated with radiotherapy only. The authors conclude that the results indicate Tbymex L can successfully prevent the harmful effects of radiation therapy on cellular immunity in **a** majority of lung cancer patients. Another study showed the effectiveness of thymostimulin in reducing the chemotoxicity of chemotherapy on 11 patients with small cell lung cancer. Patients received chemotherapy in 2 week cycles consisting of Cyclophosphamide, 4'-Epidoxoxubicin, and Etoposide for 1 week followed by Cisplatin and Etoposide for the other week. The cycle was repeated 6 times. Thymostimulin (1 mg/kg IM) was given on days 7-14 of every cycle. Responders received a maintenance treatment consisting of thymostimulin administered 1 mg/kg IM, twice weekly, until tumor relapse. Myelosuppression, fever and documented infectious episodes were significantly less severe in thymostimulin treated patients. In addition, there was significant improvement in the complete response rate and survival time of treated patients (Macchiarini 89).

In another study, thymostimulin thymus extract, used as the only therapy in otherwise untreated lung cancer patients, was able to modify alveolar lymphocyte numbers and subsets in cancer patients (Capelli 92).

Primary carcinoma of the larynx

Ten patients suffering from primary carcinoma of the larynx received thymostimutin thymus extract for 60 days following surgery for the cancer. One year follow-ups revealed a significant increase in the patients' immune response compared to controls, but no survival statistics were given (Mantovani 92).

Carcinomas of the head and neck

Combined therapy of carboplatin and radiation was compared to the same therapy plus the thymus extract thymostimulin (TP-1) in 36 patients with advanced carcinoma of the head and neck in a 2 year study. The thymostimulin treated group showed a smaller decrease in lymphocyte levels and a slightly longer disease free remission interval but had a slightly higher rate of recurrences and distant metastases. The overall rate of complete remissions was the same in both groups (94%). However, with such high percentages of complete remissions in the control group, it would be difficult to show significant differences in the treatment group (De Serdio 97). Patients with head and neck carcinoma have been shown to have deficits in cellular immunity (Balm 82, Balm 84, Cameron 84). Thymostimulin (TP-1) was used 10 days pre-operatively and 6 months post-operatively in 39 patients who underwent surgery for carcinoma of the head and neck. Another 22 patients with the same disease underwent surgical removal of the tumor only. Monocyte and drendritic cell function was restored in both treated and untreated groups following surgical removal of the tumor. However, serum low molecular mass factors (LMMF) remained elevated in both groups.. The authors concluded that the similarity of results in both groups was due to the beneficial effect of tumor removal on cellular immunity (Kerrebijn 96).

Immunohistochemical support for the use of thymus extracts in the treatment of head and neck squamous cell carcinoma has also appeared in the literature. Thymostimulin (TP-1) was administered intramuscularly in 3 different dose levels to randomly assigned groups. Group 1 (n=4) received placebo treatment; group 2 was given TP-1 at .5 mg/kg body weight

(n=4), group 3 (n=6) 1.0 mglkg and group 4 (n7-8) 2.Omg/Kg body weight for 10 consecutive days preoperatively. Histological sections of the tumor were studied using an image analysis system (VIDAS RT) to determine the concentration of T cells, macrophages, monocytes and dendritic cells for each tumor. Highly significant denser T cell infiltration into the stromal tissue area was seen in tumors removed from patients in all 3 treatment groups, i.e. all 3 TS dose levels produced significant T cell infiltration. There was also found to be a positive correlation between tumor T cell infiltration and dendritic cell capability to form clusters with T cells in the peripheral blood. Infiltration of the other immune cells studied was not significantly increased. The authors concluded that pre-operative treatment of these patients strongly enhanced T cell infiltration of tumor cells (Kerrebijn 96).

Hodgkin's disease
(lymphogranulomatosis)

Untreated patients suffering from Hodgkin's disease characteristically have defects in cellular immunity (Martelli 82). In an attempt to fortify against immune defects, t-activin, a thymus extract, was employed in a program involving 366 children afflicted with lymphogranuiomatosis (Hodgkin's disease) who also showed other immune disorders. An increase in immune parameters and a 5 year survival rate was obtained in 93.8 % of cases (Makhonova 91) compared to 70-80 % of cases treated with radiation and chemotherapy (Berkow 92, P1247).

In another study, 26 children with acute myeloid leukemia were given t-activin thymus extract treatment in addition to chemotherapy. Long term t-activin administration (no less than 2-3 years) not only reduced the incidence of intercurrent diseases, but also increased the duration of the remission period (Drozdova 90). Even in adult patients with advanced (stages M and IV) Hodgkin's disease, the administration of TFX resulted in an increased lymphocyte count and increased T cell-mediated immunity as evidenced by DTH skin tests, Erosettes and PHA responses. Improvement of hematological tolerance in patients simultaneously receiving chemotherapy or radiation therapy was also seen. This improvement came even in patients showing lymphocyte depletion (Marjanska 75, Urban 77). Another study found similar laboratory improvements using thymostimulin, another thymus extract (Martelli 82). The thymus extract thymostimulin (TP-1) was used on a small groups of patients in total remission from Hodgkin's disease. Subjects were randomly assigned to 1 of 3 groups. Group 1 (n=6) received TP-1 daily for 35 days, group 2 (n=6) received TP-1 every other day for 35 days. Both groups then received TP-1 twice a week for the following 22 weeks. Group 3 (n=7) was not treated. In the group treated daily, there was a significant increase in all T-cell fractions after 35 days. The 22 week maintenance therapy did not produce any further improvement but it did sustain the increase in T cells as a percentage and as absolute numbers. The group receiving therapy every other day showed increases in T3 and T11 cells only. Although not statistically significant, there were indications that TP-1 might also raise IL-2 and IFN-gamma levels (Liberati 88). The administration of thymus extract to patients suffering from Hodgkin's disease and simultaneous mycobacterial or viral infections was also found to be "of important supportive therapeutic value" (Skotnicki 89).

Non-Hodgkin's Lymphoma

Thymostimulin (TP-1) administered in conjunction with chemotherapeutic agents was compared to conventional chemotherapy alone in patients with intermediate and high-grade nonHodgkin's lymphoma. These patients ranged from 13 to 75 years of age and were in clinical stage II-IV or clinical stage I with bulky disease and had had no prior treatment. Of the 134 patients in the study, 68 were randomized to receive chemotherapy alone and 66 to receive chemotherapy plus TP-1. TP-1 was administered (1 mg/kg IM) daily on days 22-28 of each 28 day drug cycle to patients treated with a combination of chemotherapeutic agents known collectively as ProMACE-CytaBOM (prednisone, methotrexate, adriamycin, cyclophosphamide, etoposide, cyclophosphamide, bleomycin and oncovin (Vincristine) and on days 22-29, 50-57 and 77-85 to patients treated with the drug combination MACOP-B (methotrexate, adriamycin, cyclophosphamide, oncovin, prednisone and bleomycin). All patients also received cotrimoxazole (Bactrim^{TM}) and ketoconazole or fuconazole daily. Results showed that patients treated with TP-l plus chemotherapy had a higher complete remission rate than those treated with chemotherapy alone (59.1 % vs 42.6%) and a lower partial remission rate (21.2% vs 32.4%). Complete remission rate was most significant in patients with intermediate grade lymphomas, under 60 years of age with good hemoglobin levels. A 3 year follow-up showed no statistical difference in relapse or survival with 29 of the 68 chemotherapy alone group dead compared to 22 of the 66 in the TP-1 group. There was also no statistically significant difference between the infection rates of the 2 groups. However, the TS group actually had more infectious episodes (37 vs 17). There was also no significant difference in myelotoxicity as assessed comparing hemoglobin, white blood cell counts and platelets before and after treatment. It was not mentioned why TS was only given for 7 days before and not during chemotherapy. It was concluded that patients under 60 who had good performance scores prior to chemotherapy and normal bone marrow recovery (30-40% of all newly diagnosed non-Hodgkin's lymphoma patients) may benefit from the addition of thymic therapy (Federico 95). To the writer, an experimental design using such powerful chemotherapeutic agents - some of the most cytotoxic agents known for immune cells combined with a thymus extract used only before a

round of chemotherapy, should not be expected to produce a profound result. The significant difference in survival of patients receiving TS is surprising and encouraging.

Breast cancer

Eighty-five patients with advanced breast cancer who had previously undergone mastectomy and were currently undergoing chemotherapy, were included in a study dividing patients into 2 matching groups. One group was treated with chemotherapy and thymostimulin while the control group was treated with chemotherapy alone. The group receiving thymostimulin experienced approximately 1/2 the mild to severe leukopenia as controls. A reduction in infections, in addition to the above results, confirmed the value of immunotherapy during chemotherapy for breast cancer (Alba 91). A similar study using thymostimulin found no significant statistical differences in immunologic or haematologic values between those receiving chemotherapy alone or with thymostimulin. However, the researchers observed that administration of the thymic hormone appeared to protect the bone marrow and subjects receiving thymostimulin had a lower incidence of side effects than the untreated group (Negri 92).

Another study involving the use of thymus extracts with breast cancer included 26 women suffering from breast carcinoma who had previously undergone mastectomy 1 to 2 years before the study began. Most had also undergone curettage of the axilla. Each subject received intramuscular injections of Thymus Extract Mulli twice weekly for 4 to 6 weeks. All subjects were monitored using the carcinoembryonic antigen (CEA) test. Results showed a reduction of CEA values in approximately 70% of the cases treated with thymus extracts compared to 47% for controls. The authors concluded that because of its effectiveness and lack of side effects, immunotherapy is valuable and should be considered as a therapy in breast cancer (Reinke 85).

Note - The carcinoembryonic antigen (CEA) test is a test typically used to monitor cancers of the colon and rectum. It serves as an index of whether a particular cancer has spread, is going into remission or is recurring (Griffith 88). Although it is used to monitor colorectal cancers, it also detects breast cancers (Griffith 88, Fischbach 96).

Pavesi (Pavesi 93) reported a reduction in hematological toxicity and a favorable effect on quality of life in approximately 50 women with breast cancer, but no impact on disease outcome (time to progression or median survival time) using thymostimulin (TP-l) given 1 mg/kg body weight IM daily during chemotherapy and 3 a times week thereafter until progression or withdrawal from the study. To see if thymus extracts would be useful in counteracting the incidence of infection and myelotoxicity, patients with early breast cancer were treated with 6 rounds of a combination of cyclophosphamide, methotrexate and 5-fluorourcil combined with thymostimulin (TP-1). The patients were randomly divided into 2 groups with the treatment group of 25 receiving chemotherapy plus TP- 1 (50 mg/sqm IM) daily for 2 weeks and subsequently twice weekly for a minimum of 3 months compared to a control group of 26 patients receiving the chemotherapy alone. The results showed the TP-1 group to have statistically fewer infections (37 % vs 77 %), smaller decrease in the T4M ratio (21 % vs 46%), and fewer delays in chemotherapy protocols because of myelotoxicity (21% vs 77%). The authors noted a lower incidence of viral and fungal infections in the TP1 treated group. Their conclusion was that TP-l seemed useful for reducing the risk of infection in the early stages of breast cancer to patients subjected to chemotherapy and for allowing the administration of chemotherapy at the planned intervals without delays caused by chemotoxicity (Iaffaioli 88). Somewhat similar findings were seen in a group of 27 patients with advanced breast cancer treated with mitoxantrone and granulocyte-colony stimulating factor (G-CSF) plus the thymus extract thymostimulin (TP-I). G-CSF is an adjunct used to stimulate neutrophil production in conjunction with intensive chemotherapy when there is a high risk of a neutropenic infection. The results showed significant differences in several key haemotological toxicity indices between the TP-1 treated group and 27 controls receiving only chemotherapy. There was a significantly greater absolute neutrophil count (ANC) in the TP-1 group than in the controls as well as significantly fewer days to upgrade neutropenia to normal in patients receiving TP-l (2 vs 10 days median). The treatment group also reached acceptable levels of local site and neutrophil concentrations faster than controls. Statistically fewer patients required transfusions of ezythrocytes compared with controls (1 vs 8) and significantly fewer patients suffered from neutropenic fever (6 vs 16). The incidence (16% vs 59%), duration (5.5 vs 10 days), and severity of infection for the treatment group was also significantly lower than controls. There was, however, no difference in the response rate to chemotherapy between the 2 groups. Thymostimulin was well tolerated throughout the study (Sanchiz 96).

Colorectal and gastric cancer Thymostimulin thymus extract was used during and after surgery in 114 cases of gastric and colorectal cancer. The thymus extract was shown to be of benefit for neoplastic patients undergoing surgery to decrease the surgical stress (Ciconi 92). In another study 50 patients with inoperable colorectal cancer received TFX thymus extract injections over the course of their disease. The results showed increased granulocyte and lymphocyte counts with enhancement of cell mediated immunity, clinical improvement and increased survival time. Twelve of the cases had repeated histological examinations of the active cancer and surrounding tissue. The results showed that thymus, therapy

produced inflammatory, granulmatous and fibroblastic reactions with focal calcification and tumor necrosis. These changes are comparable to those seen in spontaneous tumor regression and are considered to be an expression of a natural host response to the invasion of neoplastic tissue (Turowsid 76, Urban 77). In situations where the colorectal cancer is operable, use of thymus extracts during and after surgery decreased the surgical stress, thereby favorably affecting the outcome (Ciconi 92).

Similar results were also reported in a 15 year review of 457 patients suffering from malignancies of the gastrointestinal tract and breast cancer. This study also showed a reduction in postoperative complications, better and accelerated wound healing, and an increased survival time compared to subjects receiving no immunotherapy (Cybulski 87). Mustacchi et al. explored the possible protective effects of thymostimulin (TP-1) on chemotherapy induced leukopenia and related febrile episodes well as possible improvement of therapeutic efficiency and tolerance when using high dose folinic acid (FA) and fluorouracil (FU) in metastatic colorectal cancer. Patients received the above chemotherapy plus TP-1 given 1 mg/kg of body weight IM per day concurrent with chemotherapy and 3 times per week thereafter until tumor progression, serious toxicity or patient refusal occurred. Results showed that the TP-1 treated group had significantly less gastrointestinal toxicity than controls. The TP-1 treated group also showed mice as many complete remissions (6 vs 3 for controls), more partial remissions (26 vs 16), fewer delays of treatment due to haemotological toxicity (46 vs 60 for controls), and fewer delays due to mucositis and diarrhea (11 vs 22). The author noted the addition of TP-1 to the fluorofolate combination improved the response rate without any significant impact on survival. Interferon (IFN) added to chemotherapy has a similar effect on response rate but does so with extremely heavy toxicity, which is virtually absent with 'his treatment regimen employing TP1 (Mustacchi 94).

Hepato-cellular cancer
There is one report of a small pilot study producing tumor regression in almost 50% of patients with hepatocellular cancer treated with thymostimulin (TP-1) alone. Further analysis revealed that Kupffer cells stimulated in vitro by TP-1 released significant amounts of tumor necrosis factor alpha and interleukin 1 alpha & 6 (Balch 97).

Melanoma
The thymus extract t-activin was given before surgery and for 6 months following surgery in 8 early stage melanoma patients. No differences were seen in the total number of T cells, T helper, T suppressor, CD38+ and CD16+ cells. Mitogenic induced lymphoproliferative responses were also unaffected. There was a slightly longer, but statistically insignificant, disease free period in the t-activin patients compared to controls who had surgery alone (17.5 vs 13 months). Although the above parameters showed no statistically significant differences, the t-activin treatment group had an overall survival time nearly twl ce that of the control group (40 vs 23 months). The authors' explanation was that there were probably other immune factors involved that were not measured. Further studies with larger groups are planned (Garashchenko 96).

Surgery

Colorectal surgery
Four-hundred-and-twenty-five patients received thymostimulin for 7 days beginning 48 hours before surgery plus cefotetan, an antibiotic, administered at the time of anesthesia. The results showed a lower incidence of post surgical infections and abscesses compared to those who received only the antibiotic, even in patients with compromised immune responses. Respiratory tract infections were ½ as frequent compared to those who received only the antibiotic (Periti 93).

Suppurative surgical infection (SSI)
Forty-seven infants with sepsis and 34 with localized infection were given t-activin thymus extract as a part of the post surgical treatment complex while 75 other infants were treated with conventional methods. Results showed that the clinical course of SSI was less severe, with more pronounced positive changes in symptoms, shortened hospital stay and decreased mortality in the treated infants. The authors confirmed that the postoperative use of thymus extracts in infants leads to an increase in the number and functional capacity of peripheral T-lymphocytes with improved bactericidal activity of circulating phagocytes in postoperative newborns with SSI (Samsygin 89).

Post-operative Sepsis
The thymus extracts thymalin and t-activin were used in a study involving post-operative sepsis. The authors reported after 14 days of treatment that thymalin stimulated T cells while acting with immunoglobulins. T-activin increased the numbers of T cells and B cells. Clinical improvement was best when the thymus extracts were used in combination with other medication (Bulava 96). After citing immunologic and clinical studies demonstrating that immunodeficiency states are the most probable causes the post-operative complications following reparative surgery of the facial bones, results were

presented for 10 cases of facial surgery for congenital and acquired deformation using t-activin conjointly with surgery. This protocol normalized immune parameters and prevented development of postoperative complications (Volozhin 96).

Orthopedic implants
Teicoplanin, a thymus extract, was shown to be a useful prophylactic against infection resulting from orthopedic implant surgery. Deep prosthetic infections are very difficult to cure without removing the infected device; the outcome can be devastating, such as: total loss of joint function, amputation, and occasionally, death. Preliminary results show that teicoplanin has a role to play both in treatment of infection and prophylaxis against hospital-acquired infection (Periti 92).

Abdominal surgery
Sixty-one patients who had been previously classified as anergic undement elective abdozninal surgery in conjunc tion with simultimousl receiving thymostimulin thymus extract. The authors found **a** notable reduction of Postoperative infection in the treated group when compared with 62 controls who were anergic and underwent surgery but received no therapy (Perotti 47).

Surgery with the immunocompromised
Two-hundred-and-twelve surgical patients at risk because they were immunocompromised were divided into 2 homogeneous groups: the treatment group which received thymostimulin thymus extract during and after surgery, and the control group which received conventional surgical treatment. All patients were affected by severe pathologies. Positive results were obtained in the thymostimulin treated group in terms of reduced morbidity, Postoperative hospitalization and mortality as compared to controls. The author's conclusion was that treatment with thymostimulin in immunocompromised patients is an important factor in avoiding or reducing Postoperative infection rates (Lai 92).

Immunosenescence (Immune Effects of **Aging)**
A strong and vigorous immune system is especially important in the health of the elderly. The lifestyles of most older persons in our society compromise immunity in many ways. Several of the common causes of compromised immunity listed earlier in this paper are especially relevant to aging persons. As a group, older people tend to exercise less, consume more prescription and nonpresciption drugs, and are exposed to more medical procedures. Suboptimal nutritional intake is also a common problem associated with aging. These stressors occur at a time of life in which inadequate digestion and elimination combined with decreased liver function compound their detrimental effects on immune function. Because these conditions are additive and cumulative, it is difficult to determine exactly how much of the aging in humans is due to the natural physical process and how much is incurred by lifestyle components that lead to compromised immunity. Even though the exact proportion may be difficult to assess, it is no coincidence that many of the causes of compromised immunity are also involved in aging. "The programmed decline in physiologic competence, which we know as aging, is in fact a series of concomitant changes primarily manifested in the immune system" (Weksler 81).

One of the most consistent findings associated with immunosenescence in humans and animals is a decline in T cell numbers, function and proliferation as aging increases. This has been attributed to the involution of the thymus gland (Kouttab 89) and the subsequent decreased production of the thymic hormones that control T lymphocyte numbers and function (Ghanta 90). These decrease with age and are associated with a "thymic menopause" and cellular immune senescence contributing to the development of diseases in the aged (Hadden 92). The consequence of this process is an increased susceptibility to infections, autoimmune diseases and cancer (Weksler 81). Liquid thymus extracts have been used to help restore cellular immunity, including the number and function of T-lymphocytes (Skotnicki 89, Kouttab 89, Hadden 89, Dabrowski 80, Segatta 86, Park 84, Poli 86, Periti 93, Harrower 32, Weksler 91). The question is whether liquid thymus extracts can do the same in the elderly person.

There is scant literature on the clinical and direct immunological effects of liquid thymus extracts in the aged. In one of the few studies, Pandolfi et al. administered thymostimulin (TP-1) to 14 randomly selected persons averaging 80 years of age who were free of neoplastic, autoimmune or infectious diseases at the time of selection and had a normal lymphocyte count (Pandolfi 83). Dosage was 1 mg/kg per wk for 1 month followed by 1 mg/kg per 2 weeks for 2 months. The total treatment time was 90 days. The results were compared to a control group of 12 subjects receiving no therapy. Routine blood, urine and clinical data were evaluated before therapy, at 90 days and at 180 days. The study found no change in the absolute lymphocyte count. There was an increase in T lymphocyte resetting but it was not statistically significant due to the small N size. The only statistically significant difference in laboratory measurement between the two groups was a decrease in the sedimentation rate from a slightly elevated value of 22 before therapy began to 12 at 180 days for the treatment group, a decrease of about 50%. The clinical results of the study, however, were much more striking. Significantly fewer patients in the treated group had infections than controls (21 % vs. 67 %). In addition, there was only 1 episode of urinary tract infection in the treated group compared to 6 in the controls and only 2 episodes of respiratory infection in the treated group

compared to 11 in the control group. No other infections in the treated group occurred, but there were 4 in the controls. No side effects or toxicities were reported.

Because no true T lymphocyte function tests were completed, we can only surmise that the cause of this improved resistance to infection may have been due to increased T cell function, as has been shown by previous studies in humans and animals (Kouttab 89, Stankiewiez 86, Dabrowski 80, Segatto 86, Park 84, Poli 86). The results of this study provide a very interesting indication that thymus extracts may not significantly increase lymphocyte numbers in relatively normal, healthy elderly persons but may significantly alter their clinical course, even when their lymphocyte count is normal. Studies presented earlier in this paper demonstrated the beneficial effects thymus extracts in treating the most common diseases associated with aging: infections, autoimmune diseases and cancer. The study presented above, however, demonstrates the possibility of benefits of liquid thymus extracts given to elderly subjects on a prophylactic basis. Although the increased clinical response was probably due, at least in part, to the increased functional capabilities of T lymphocytes, there may also have been other factors involved. The thymus appears to be involved in decreasing some of the normal processes of aging in association with other organs and systems. In other words, they may to have extra-immunological functions as well (Fabris 90,Czaplicki 89).

For example, studies have shown the beneficial effects of liquid thymus extracts on the structure and function of livers in aging animals. Typically, the hepatocyte nuclei of livers in aging animals increase in size. Mitochondria are also swollen and have deficient membrane composition with dark and electron dense internal structures. The rough endoplasmic reticulum (RER) and smooth endoplasmic reticulum (SER) also show characteristic patterns of degeneration. These characteristic changes should be taken as a criterion of aging and diminished biological activity (Weindruch 80). Fetal thymic calf extracts have been shown to induce a significant decrease in the size of hepatocyte nuclei in aging (450 day old) mice (Czaplild 90). Microscopic examination of hepatocyte mitochondria from treated mice showed the histological picture of healthy young mice. In contrast, histology of hepatocytes from the control group showed the typical pattern of degeneration associated with aging. In another study, thymus peptides (thymic factor D) extracted from swine and injected into 24 month old rats (senescent rats) in a dosage of 2 mg/kg every other day for 3 months resulted in decreased liver content of malondialdehyde & lipofusion accompanied by increased liver glutathione peroxidase (GSH) levels. Microscopic examination revealed that hepatic mitochondrial and microsomal membranes of these aged rats had recovered to be like those of young adult rats (Chung-Kuo 93). Another finding from this study was that liver and spleen function did not deteriorate with age in the treated animals. Other studies have shown decreased levels of unsaturated fatty acid peroxides in cerebral and splenic tissue of adult rodents (Czaplicld 89). Histologies of these animals revealed the preservative and anti-aging effects of embryonic and early fetal calf thymus extracts. The authors, conclusion was that the active substances produced by embryonal thymus and early fetal thymus not only affect the immunological system, but also interfere with the process of organ aging. Investigators have reported that the administration of liquid thymus extracts has been associated with the disappearance of presbyopia and climacteric changes in elderly persons (Kaliuzhnaia 89). Other investigators demonstrated that thymus extracts significantly increased the longevity of treated mice (Hadden 89, Kaliuzhnaia 89).

Taken as a group, these studies indicate that liquid thymus extracts may be useful in preserving antioxidant activity, may decrease the typical response to aging in the liver and possibly other organs, and may influence longevity in some animals. 'Ihe thymus is also fundamental to the integration and proper interaction between the immune, endocrine and central nervous systems (CNS). There is recent evidence that indicates the thymus plays an indirect but considerable role within the neuroendocrine network. A number of homeostatic processes governed by the hypothalamopituitary axis are involved, including regulation of tissue metabolism (Fabris 90, Dabrowski 90).

In summary, decreased cellular immunity is directly associated with increased aging. Liquid thymus extracts have been shown to be beneficial in some clinical conditions affecting the elderly. They have been shown to have extraimmunological benefits on other organs and systems. The use of thymus extracts may be an important, but overlooked, option in treating and possibly preventing many clinical conditions of the aging person.

Miscellaneous

Burns

Opportunistic micro-organisms causing infections in burn patients are often acquired in hospitals. These infections commonly involve Gram-positive organisms which may be resistant to several antibiotics. Teicoplanin, alone and in combination with additional antibacterial drugs, proved effective in the treatment of Gram-positive infections of various types in hospitalized burn patients (Periti 92).

In another study the thymus extract t-activin was used in combination with sodium nucleinate plus lidocaine to restore phagocytic function of peripheral blood lymphocytes and increase humoral immunity in severely burned animals. Treatment decreased colonization of pseudomonas aeurginosa and candida pathogens and decreased the death rate (Shatalova 97).

Preeclampsia and eclampsia
Progressive immune depression accompanied by a parallel drop in parathyroid hormone level to critical values has been demonstrated in patients with eclampsia. Patients with pre-eclampsia delivering by cesarean section were treated post-operatively with the thymus extract, t-activin. Cellular immunity was compared with patients receiving no t-activin. A marked immuno-stimulatory effect of the thymus extract on T-lymphocytes and especially on theophylline-resistant T-lymphocyte subpopulations was observed. The effect of t-activin was most marked on the 3rd to 5th day of the postoperative period (Iamiushina 92).

Male Infertility
In an unusual 2 part study, the effect of complete thymic extract on the motility and progression of sperm from men with previously confirmed asthenozoospermia was invetigated. In the first part, the thymic extract was incubated in vitro with sperm obtained from men with asthenozoospermia and compared to untreated in vitro sperm from the same men. In the second part of the study, 10 men with asthenozoospermia were given injections of the thymic extract (150mg/day IM) for 7 days and sperm samples were compared before and after therapy. In both parts of this study results showed a significant increase in sperm motility and progression with the introduction of complete thymic extract (Arsenijevic 96).

Cardiac Function
In a 4 year study comparing treatments for men with biopsy proven myocarditis or dilated cardiomyopathy 13 men were treated with thymomodulin plus conventional treatment, 13 with interferon-alpha plus conventional treatment, and 12 with conventional treatment alone for a period of 2 years. Results at the 2 year follow-up showed significant improvement in left ventricular ejection fraction (81% vs 66%), and maximum exercise time (5 vs 3 minutes) during exercise. At the 2 year follow-up, 88% of the men in the 2 treatment groups had normal electrocardiogram compared with 22% of the controls, and 73% had improved their functional class compared to 25% of the men in the control group (Muric 96).

Side Effects
Over 200 articles were reviewed in the preparation of this paper. One of the most striking consistencies throughout the many articles was the absence of harmful side effects produced by thymus extracts. Except for two incidents of toxicity (see "Toxicities" section), no hazardous side effects were listed, even in the studies involving injections. A few authors noted the lack of harmful side effects. This is unusual in medical literature, especially in new or experimental therapies. one review article found “a complete lack of detrimental side effects" in over 50 studies it reviewed (Kouttab 89). Beneficial side effects are not usually measured or reported in clinical experiments, however, one study reported a decreased sensitivity to viral and bacterial infections and an improvement in the general clinical state and overall well-being of subjects linking a thymus extract (Skotnicki 89). Some studies used thymus extracts to decrease the iatrogenic side effects and toxicity of radiotherapy, chemotherapy and surgery (Vuckovic 92, Alba 91, Negri 92).

Toxicities
Only 2 toxicities were reported in all of the papers referenced here or in any of the other papers reviewed. This is an important finding, particularly when compared to the side effects and toxicities of some of the drugs used to treat the same conditions that thymus extracts have successfully treated, especially in the fral or chronically ill patient. One study, however, showed a severe anaphylactic reaction to thymostimulin. This was a report of a single 36 year-old male receiving thymostimulin as part of the treatment for a neck tumor. In this unusual case, the man showed an anaphylactic response on the first injection. Subsequent tests showed no slum response to bovine material but a response specific to the thymostimulin (Marcos 91). In light of tins we would suggest routine skin tests before injection of any thymus extracts as a precautionary measure.

Contraindications
Although none have been reported, all patients with an organ transplant or other forms of allografts (same species, different genetic strain) or xenografts (different species) must be cautious of any agent capable of stimulating a cellular immune response as there is the potential risk of increasing the graft-versus-host response rejection rate of implants. Orthopedic implants, however, may be an exception as the study noted above successfully used a thymus extract to prevent complications of orthopedic implant surgery and reported no increase of implant rejection (Periti 92).

Summary

Thymus extracts have been shown to be of significant therapeutic value using both clinical and laboratory indices. It is important to note that the improvements taking place in several of these experiments were not just palliative improvements. In some studies there were indications of an actual reconstitution of the cellular immune system as indicated by the increase in the numbers of T lymphocytes (Skotnicki 89, Kouttab 89, Hadden 89, Stankiewiez 86), macrophages (Andolina 87) and suppressor cells (Kouttab 89) and a restoration of function of these and other cells as shown by: increased conversion of immature thymocytes to non-dedicated T cells in human bone marrow (Kouttab 89); enhanced proliferation response to concanavalan A (Con A) (Dabrowski 80) and phytohemagglutinin (PRA) (Segatto 86, Poli 86, Vuckovic 92, Marjanska 75); increased E-rosette formation (Macchiarini 89); increased phagocytosis and bactericidal activity of circulating phagocytes (Kartasheva 91, Samsygin 89, Alba 91), increased numbers of macrophages and monocytes (Kouttab 89, Tas 90); decreased caminoembryonic antigen (CEA) levels in cancer patients (Reinke 85); and a restoration of skin test responsiveness (DTH response) in previously unresponsive patients (Kouttab 89, Lasisz 90, Periti 93, Marjanska 75). Laboratory tests have also confirmed the favorable effects of thymus extracts on humoral immunity as shown by: an increase in the B lymphocytes (Twomey 82) and serum immunoglobulins to normal (Kouttab 89); an increase in depressed salivary IgA levels (Fiocchi 86); and a down regulation of elevated IgE (Kouttab 89, Fiocchi 87, Bagnato 89, Cavagni 89) and eosinophil counts (Kouttab 89, Fiocchi 87).

The positive effects of thymus extracts have even been demonstrated in laboratory tests for autoimmune reactions by reducing rheumatoid factor alpha 2 and serum G globulin levels (Skotnicki 89, Skotnicki 86, Lasisz 90) with an accompanying rise in depressed hemoglobin and serum iron levels as the autoimmune factors decreased (Skotnicki 86). The ability to affect these multifactor autoimmune reactions provides further indications that the regulatory mechanisms modified by thymic extracts are systemic. Their effects do not come from just focal inhibition or stimulation of a single mechanism. This broad range of laboratory indices taken as a whole indicates that thy extracts are capable of affecting the immune response at a fundamental level.

One of the most striking features of therapy using thymus extracts is the wide variety of conditions in which these extracts have been successfully employed. They have been used orally and as injectables; by themselves and in combination with other-therapeutics. In some instances, they have been the only effective treatment. These extracts have been successfully used clinically to prevent and treat primary and secondary infections (Kartasheva 91, Periti 92), prevent relapses (Kouttab 89) and secondary complications of infections (Kartasheva 91), and to reduce postoperative infection rates (Lai 92). They have also been used to: modulate the deleterious effects of radiotherapy, chemotherapy and surgery (Vuckovic 92, Alba 91, Negri 92); accelerate the rate of wound healing (Skotnicki 89); decrease some of the effects of aging (Czapliki 90, Chung-Kuo 93); improve the efficacy of other treatments (Grigor'ev 89); and as an adjuvant in surgery (Periti 93, Samsygin 89, Periti 92, Lai 92) and treatments using antifungal, antibiotic and antiviral agents (Skotnicki 89, Radomska 87, Czaplicki 89, laniushina 92, Gilman 87, Drews 84).

Few medicines can boast effectiveness in treating conditions so diverse as: infections [deep disseminated (Dworniak 91), or focalized (Grismondi 91) of bacterial (Guliamov 91) and viral (Kicka 86, Dworniak 91, Zeman 91, Skotnicki 84) origins;respiratory diseases [infectious (Kouttab 89, Fiocchi 96), non-infectious (Stankiewiez 86, Matusiewicz 87, Gieldanowski 81, Smogorzewska 84), acute (Stankiewiez 86) and chronic (Gieldanowsiki 81, Smogorzewska 84, Frolov 92, Tortorella 92.)]; diseases of immunodeficiency (Davies 82, Valesini 87), autoimmunity (Skotnicki 84, Kartasheva 91, Suchkova 90); allergies (Chachoua 89); degenerative skin diseases (Skotnicki 89, Kouttab 89, Pecora 91, Cavagni 89, Kaliuzhnaia 89); as well as neoplasias of the lung (Capelli 92), larynx (Mantovani 92), leukocytes (Skotnicki 89, Martelli 82, Makhonova 91, Drozdova 90, Marjanska 75), breast (Alba 91, Negri 92, Reinke 85, Griffith 88) and of colorectal and gastric origin (Ciconi 92, Urban 77, Cybulski 87). They have also been shown to be of benefit in increasing the survival time of patients with severe or terminal illnesses (Kartasheva 91, Cybulski 87, Samsygin 89, Periti 92).

In some cases these results persisted long after the treatment was discontinued. This indicates that it was effective in changing the natural course of the disease by working at the causative level, i.e., the faulty immune process rather than at the combative (antibiotics) or symptomatic (bronchodilators, etc.) levels. In others cases, the change was seen only while the extracts were being administered indicating that even though these extracts were not effective at the causal level, they were still able to play a significant role in the therapeutic regimen and, at the least, provide an improvement in the clinical state and general well-being of the patient (Skotnicki 89). The combined results of the many studies on the various thymus extracts, taken as a group, is very encouraging and appears to offer a possible new alternative and/or adjunct to present therapies. Individually, many of the studies showed design weaknesses. Small N-size plagued most of these studies with as few as 4 subjects in some. In several studies there was no randomization of groups and in a few, no control groups. Only a few of the studies used double-blind trials. Although there is a need for better designed studies, the

combined results and the variety of health conditions reported to respond to the thymus extracts tested Provide enough material to consider thymus extracts as a potentially promising and useful new area of treatment and research.

In summary, thymus extracts have been shown to be extremely versatile from other areas of influence are probable. Some of the most severe clinical conditions showed the most profound recovery. Thymus extracts were beneficial in nearly all studies with a degree of efficiency varying from symptomatic relief to curative. The overall clinical impact was extremely positive with no reports of undesirable side effects and only 2 toxicities. The favorable clinical response combined with the lack of side effects or toxicity makes the use of thymus extracts a potential height and research option that has yet to be recognized on this continent.

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