Influenza Virus (Flu)
Updated: 08/26/2004

ABSTRACTS

Lactoferrin immunomodulation of DTH response in mice.

Actor JK, Hwang SA, Olsen M, et al.

Int Immunopharmacol. 2002 Mar; 2(4):475-86.

Improved nontoxic adjuvants, especially adjuvants capable of inducing cell-mediated immunity (CMI), are needed for research in immunology and for development of human and veterinary vaccines. Bovine Lactoferrin, an effector molecule shown to directly participate in host defense, was assessed at various concentrations as an adjuvant component for induction of DTH responses to sheep red blood cells (SRBC). Subcutaneous immunization with Lactoferrin enhanced delayed type hypersensitivity (DTH) in CBA mice in a dose-dependent fashion; DTH responses were most significantly increased when sensitization was accomplished using Lactoferrin at 50 microg/dose and 250 microg/dose. Furthermore, Lactoferrin admixed with suboptimal dose of SRBC enhanced DTH responses by over 17-fold. Peritoneal cells collected from mice intraperitoneally injected with a 100 microg/dose of Lactoferrin demonstrated modest, but significant, production of TNF-alpha, IL-12 and MIP-1alpha when cultured in vitro, compared to saline-injected controls. J774A.1 murine macrophages stimulated with Lactoferrin resulted in increased TNF-alpha protein production, and upregulated IL-12 and IL-15 mRNA. Levels of message for chemokines MIP-1alpha and MIP-2 were also increased in a dose-dependent way. Taken together, these results indicate that Lactoferrin as an adjuvant may stimulate macrophages to generate a local environment likely to push immune responses towards development and maintenance of CMI

The effect of Sambucol, a black elderberry-based, natural product, on the production of human cytokines: I. Inflammatory cytokines.

Barak V, Halperin T, Kalickman I.

Eur Cytokine Netw. 2001 Apr; 12(2):290-6.

Sambucus nigra L. products - Sambucol - are based on a standardized black elderberry extract. They are natural remedies with antiviral properties, especially against different strains of influenza virus. Sambucol was shown to be effective in vitro against 10 strains of influenza virus. In a double-blind, placebo-controlled, randomized study, Sambucol reduced the duration of flu symptoms to 3-4 days. Convalescent phase serum showed a higher antibody level to influenza virus in the Sambucol group, than in the control group. The present study aimed to assess the effect of Sambucol products on the healthy immune system - namely, its effect on cytokine production. The production of inflammatory cytokines was tested using blood - derived monocytes from 12 healthy human donors. Adherent monocytes were separated from PBL and incubated with different Sambucol preparations i.e., Sambucol Elderberry Extract, Sambucol Black Elderberry Syrup, Sambucol Immune System and Sambucol for Kids. Production of inflammatory cytokines (IL-1 beta, TNF-alpha, IL-6, IL-8) was significantly increased, mostly by the Sambucol Black Elderberry Extract (2-45 fold), as compared to LPS, a known monocyte activator (3.6-10.7 fold). The most striking increase was noted in TNF-alpha production (44.9 fold). We conclude from this study that, in addition to its antiviral properties, Sambucol Elderberry Extract and its formulations activate the healthy immune system by increasing inflammatory cytokine production. Sambucol might therefore be beneficial to the immune system activation and in the inflammatory process in healthy individuals or in patients with various diseases. Sambucol could also have an immunoprotective or immunostimulatory effect when administered to cancer or AIDS patients, in conjunction with chemotherapeutic or other treatments. In view of the increasing popularity of botanical supplements, such studies and investigations in vitro, in vivo and in clinical trials need to be developed

Prospects of the clinical utilization of melatonin.

Bubenik GA, Blask DE, Brown GM, et al.

Biol Signals Recept. 1998 Jul; 7(4):195-219.

This review summarizes the present knowledge on melatonin in several areas on physiology and discusses various prospects of

its clinical utilization. Ever increasing evidence indicates that melatonin has an immuno-hematopoietic role. In animal studies, melatonin provided protection against gram-negative septic shock, prevented stress-induced immunodepression, and restored immune function after a hemorrhagic shock. In human studies, melatonin amplified the antitumoral activity of interleukin-2. Melatonin has been proven as a powerful cytostatic drug in vitro as well as in vivo. In the human clinical field, melatonin appears to be a promising agent either as a diagnostic or prognostic marker of neoplastic diseases or as a compound used either alone or in combination with the standard cancer treatment. Utilization of melatonin for treatment of rhythm disorders, such as those manifested in jet lag, shift work or blindness, is one of the oldest and the most successful clinical application of this chemical. Low doses of melatonin applied in controlled-release preparation were very effective in improving the sleep latency, increasing the sleep efficiency and rising sleep quality scores in elderly, melatonin-deficient insomniacs. In the cardiovascular system, melatonin seems to regulate the tone of cerebral arteries; melatonin receptors in vascular beds appear to participate in the regulation of body temperature. Heat loss may be the principal mechanism in the initiation of sleepiness caused by melatonin. The role of melatonin in the development of migraine headaches is at present uncertain but more research could result in new ways of treatment. Melatonin is the major messenger of light-dependent periodicity, implicated in the seasonal reproduction of animals and pubertal development in humans. Multiple receptor sites detected in brain and gonadal tissues of birds and mammals of both sexes indicate that melatonin exerts a direct effect on the vertebrate reproductive organs. In a clinical study, melatonin has been used successfully as an effective female contraceptive with little side effects. Melatonin is one of the most powerful scavengers of free radicals. Because it easily penetrates the blood-brain barrier, this antioxidant may, in the future, be used for the treatment of Alzheimer's and Parkinson's diseases, stroke, nitric oxide, neurotoxicity and hyperbaric oxygen exposure. In the digestive tract, melatonin reduced the incidence and severity of gastric ulcers and prevented severe symptoms of colitis, such as mucosal lesions and diarrhea

Effect of vitamin and trace-element supplementation on immune responses and infection in elderly subjects.

Chandra RK.

Lancet. 1992 Nov 7; 340(8828):1124-7.

Ageing is associated with impaired immune responses and increased infection-related morbidity. This study assessed the effect of physiological amounts of vitamins and trace elements on immunocompetence and occurrence of infection-related illness. 96 independently living, healthy elderly individuals were randomly assigned to receive nutrient supplementation or placebo. Nutrient status and immunological variables were assessed at baseline and at 12 months, and the frequency of illness due to infection was ascertained. Subjects in the supplement group had higher numbers of certain T-cell subsets and natural killer cells, enhanced proliferation response to mitogen, increased interleukin-2 production, and higher antibody response and natural killer cell activity. These subjects were less likely than those in the placebo group to have illness due to infections (mean [SD] 23 [5] vs 48 [7] days per year, p = 0.002). Supplementation with a modest physiological amount of micronutrients improves immunity and decreases the risk of infection in old age

Natural killer cells from aging mice treated with extracts from Echinacea purpurea are quantitatively and functionally rejuvenated.

Currier NL, Miller SC.

Exp Gerontol. 2000 Aug; 35(5):627-39.

A growing body of anecdotal evidence in young and adult humans suggests that certain phytochemicals have the capacity to ameliorate tumors and reduce infections, especially those mediated by virus, in vivo. These indications prompted us, therefore, to investigate the potentially immuno-stimulating effect of one such phytocompound, Echinacea purpurea, on natural killer (NK) cells since these cells are active in spontaneous, non-specific immunity against neoplasms and virus-mediated infections. We elected to study aging mice, since, at this stage of life, like humans, the above-mentioned afflictions increase in frequency. We had previously found that neither the cytokine, interleukin-2, nor the pharmacological agent, indomethacin, both potent stimulators of NK cell numbers/function in younger adult mice, was effective in stimulating NK cells in elderly mice. The present study was designed to assess the numbers/production of NK cells in the spleen and bone marrow of aging, normal mice, after in vivo dietary administration of E. purpurea (14 days), or, after injection of thyroxin, a stimulant of NK cell function (10 days). Immunoperoxidase labeling techniques, coupled with hematologic tetrachrome staining were used to identify NK cells in both the spleen (primary site of NK cell function) and the bone marrow (site of NK cell generation). Double immunofluorscence staining, employing propidium iodide, was used to assess NK cell lytic function. Our results revealed that E. purpurea, but not thyroxin, had the capacity to increase NK cell numbers, in aging mice, reflecting increased new NK cell production in their bone marrow generation site, leading to an increase in the absolute numbers of NK cells in the spleen, their primary destiny. The E. purpurea-mediated increase in NK cell numbers was indeed paralleled by an increase in their anti-tumor, lytic functional capacity. Collectively, the data indicate that E. purpurea, at least, and possibly other plant compounds, appear to contain phytochemicals capable of stimulating de novo production of NK cells, as well as augmenting their cytolytic function, in animals of advanced age

Therapeutic potential of glutathione.

Exner R, Wessner B, Manhart N, et al.

Wien Klin Wochenschr. 2000 Jul 28; 112(14):610-6.

Reactive oxygen species, formed in various biochemical reactions, are normally scavenged by antioxidants. Glutathione in its reduced form (GSH) is the most powerful intracellular antioxidant, and the ratio of reduced to oxidised glutathione (GSH:GSSG) serves as a representative marker of the antioxidative capacity of the cell. Several clinical conditions are associated with reduced GSH levels which as a consequence can result in a lowered cellular redox potential. GSH and the redox potential of the cell are components of the cell signaling system influencing the translocation of the transcription factor NF kappa B which regulates the synthesis of cytokines and adhesion molecules. Therefore, one possibility to protect cells from damage caused by reactive oxygen species is to restore the intracellular glutathione levels. Cellular GSH concentration can be influenced by exogenous administration of GSH (as intravenous infusion or as aerosol), of glutathione esters or of GSH precursors such as glutamine or cysteine (in form of N-acetyl-L-cysteine, alpha-lipoic acid). The modulation of GSH metabolism might present a useful adjuvant therapy in many pathologies such as intoxication, diabetes, uremia, sepsis, inflammatory lung processes, coronary disease, cancer and immunodeficiency states

Effect of micronutrient supplementation on infection in institutionalized elderly subjects: a controlled trial.

Girodon F, Lombard M, Galan P, et al.

Ann Nutr Metab. 1997; 41(2):98-107.

To determine the impact of a trace element and vitamin supplementation on infectious morbidity, a double-blind controlled trial was performed on 81 elderly subjects in a geriatric center during a 2-year period. Subjects were randomly assigned to one of four treatment groups, and received daily: placebo; trace elements/zinc 20 mg; selenium 100 micrograms); vitamins (vitamin C 120 mg; beta-carotene 6 mg; alpha-tocopherol 15 mg); or a combination of trace elements and vitamins at equal doses. (1) Before supplementation, low serum values in vitamin C, folate, zinc and selenium were observed in more than two thirds of the patients. (2) After 6 months of supplementation, a significant increase in vitamin and trace element serum levels was obtained in the corresponding treatment groups: a plateau was then observed for the whole study. (3) Subjects who received trace elements (zinc and selenium) alone or associated with vitamins had significantly less infectious events during the 2 years of supplementation. These results indicate that supplementation with low doses of vitamins and trace elements is able to rapidly correct corresponding deficiencies in the institutionalized elderly. Moreover, zinc and selenium reduced infectious events

Impact of trace elements and vitamin supplementation on immunity and infections in institutionalized elderly patients: a randomized controlled trial. MIN. VIT. AOX. geriatric network.

Girodon F, Galan P, Monget AL, et al.

Arch Intern Med. 1999 Apr 12; 159(7):748-54.

BACKGROUND: Antioxidant supplementation is thought to improve immunity and thereby reduce infectious morbidity. However, few large trials in elderly people have been conducted that include end points for clinical variables. OBJECTIVE: To determine the effects of long-term daily supplementation with trace elements (zinc sulfate and selenium sulfide) or vitamins (beta carotene, ascorbic acid, and vitamin E) on immunity and the incidence of infections in institutionalized elderly people. METHODS: This randomized, double-blind, placebo-controlled intervention study included 725 institutionalized elderly patients (>65 years) from 25 geriatric centers in France. Patients received an oral daily supplement of nutritional doses of trace elements (zinc and selenium sulfide) or vitamins (beta carotene, ascorbic acid, and vitamin E) or a placebo within a 2 x 2 factorial design for 2 years. MAIN OUTCOME MEASURES: Delayed-type hypersensitivity skin response, humoral response to influenza vaccine, and infectious morbidity and mortality. RESULTS: Correction of specific nutrient deficiencies was observed after 6 months of supplementation and was maintained for the first year, during which there was no effect of any treatment on delayed-type hypersensitivity skin response. Antibody titers after influenza vaccine were higher in groups that received trace elements alone or associated with vitamins, whereas the vitamin group had significantly lower antibody titers (P<.05). The number of patients without respiratory tract infections during the study was higher in groups that received trace elements (P = ".06)." Supplementation with neither trace elements nor vitamins significantly reduced the incidence of urogenital infections. Survival analysis for the 2 years did not show any differences between the 4 groups. CONCLUSIONS: Low-dose supplementation of zinc and selenium provides significant improvement in elderly patients by increasing the humoral response after vaccination and could have considerable public health importance by reducing morbidity from respiratory tract infections

The effectiveness of vitamin C in preventing and relieving the symptoms of virus-induced respiratory infections.

Gorton HC, Jarvis K.

J Manipulative Physiol Ther. 1999 Oct; 22(8):530-3.

BACKGROUND: An ever increasing demand to evaluate the effect of dietary supplements on specific health conditions by use of a "significant scientific" standard has prompted the publication of this study. OBJECTIVE: To study the effect of megadose Vitamin C in preventing and relieving cold and flu symptoms in a test group compared with a control group. DESIGN: Prospective, controlled study of students in a technical training facility. SUBJECTS: A total of 463 students ranging in age from 18 to 32 years made up the control group. A total of 252 students ranging in age from 18 to 30 years made up the experimental or test group. METHOD: Investigators tracked the number of reports of cold and flu symptoms among the 1991 test population of the facility compared with the reports of like symptoms among the 1990 control population. Those in the control population reporting symptoms were treated with pain relievers and decongestants, whereas those in the test population reporting symptoms were treated with hourly doses of 1000 mg of Vitamin C for the first 6 hours and then 3 times daily thereafter. Those not reporting symptoms in the test group were also administered 1000-mg doses 3 times daily. RESULTS: Overall, reported flu and cold symptoms in the test group decreased 85% compared with the control group after the administration of megadose Vitamin C. CONCLUSION: Vitamin C in megadoses administered before or after the appearance of cold and flu symptoms relieved and prevented the symptoms in the test population compared with the control group

Antimicrobial properties of Allium sativum (garlic).

Harris JC, Cottrell SL, Plummer S, et al.

Appl Microbiol Biotechnol. 2001 Oct; 57(3):282-6.

Although garlic has been used for its medicinal properties for thousands of years, investigations into its mode of action are relatively recent. Garlic has a wide spectrum of actions; not only is it antibacterial, antiviral, antifungal and antiprotozoal, but it also has beneficial effects on the cardiovascular and immune systems. Resurgence in the use of natural herbal alternatives has brought the use of medicinal plants to the forefront of pharmacological investigations, and many new drugs are being discovered. This review aims to address the historical use of garlic and its sulfur chemistry, and to provide a basis for further research into its antimicrobial properties

[Preventive action of an immunomodulator on respiratory infections in elderly subjects].

Hugonot R, Gutierrez LM, Hugonot L.

Presse Med. 1988 Jul 27; 17(28):1445-9.

Three hundred and fourteen elderly subjects admitted to chronic medical centers were given either RU 41740 (n = 155) or a placebo (n = 159) at the rate of one course per month during three months. RU 41740 was administered in doses of 2 mg per day during 8 days in the first course and 1 mg per day during 8 days in the second and third courses. The subjects were followed up and regularly examined every three months for one year. The incidence of acute infectious episodes was evaluated in both groups. Compared to those patients who received the placebo, the number of subjects without infection was significantly higher in the treated group during the 0-6 months and the 0-9 months periods and during the 12 months of observation. The number of infectious episodes was reduced during the 0-3 months and 0-9 months periods and throughout the 12 months of the trial. The mean duration of pulmonary infections that occurred during the 0-6 and 0-9 months periods was reduced. Finally, there was a significant decrease in the duration of antibiotic therapy during the 0-3, 0-6, 0-9 months periods and during the 12 months of observation. The drug was well tolerated. This study showed that RU 41740 is effective in protecting elderly and therefore fragile subjects against respiratory infections

Curcumin inhibits Th1 cytokine profile in CD4+ T cells by suppressing interleukin-12 production in macrophages.

Kang BY, Song YJ, Kim KM, et al.

Br J Pharmacol. 1999 Sep; 128(2):380-4.

1 Interleukin-12 (IL-12) plays a central role in the immune system by driving the immune response towards T helper 1 (Th1) type responses which are characterized by high IFN-gamma and low IL-4 production. In this study we investigated the effects of curcumin, a natural product of plants obtained from Curcuma longa (turmeric), on IL-12 production by mouse splenic macrophages and the subsequent ability of these cells to regulate cytokine production by CD4+ T cells. 2 Pretreatment with curcumin significantly inhibited IL-12 production by macrophages stimulated with either lipopolysaccharide (LPS) or head-killed Listeria monocytogenes (HKL). 3 Curcumin-pretreated macrophages reduced their ability to induce IFN-gamma and increased

the ability to induce IL-4 in Ag-primed CD4+ T cells. Addition of recombinant IL-12 to cultures of curcumin-pretreated macrophages and CD4+ T cells restored IFN-gamma production in CD4+ T cells. 4 The in vivo administration of curcumin resulted in the inhibition of IL-12 production by macrophages stimulated in vitro with either LPS or HKL, leading to the inhibition of Th1 cytokine profile (decreased IFN-gamma and increased IL-4 production) in CD4+ T cells. 5 These findings suggest that curcumin may inhibit Th1 cytokine profile in CD4+ T cells by suppressing IL-12 production in macrophages, and points to a possible therapeutic use of curcumin in the Th1-mediated immune diseases

Melatonin administration and pituitary hormone secretion.

Kostoglou-Athanassiou I, Treacher DF, Wheeler MJ, et al.

Clin Endocrinol (Oxf). 1998 Jan; 48(1):31-7.

OBJECTIVE: The relationship between the pineal gland and pituitary function remains controversial, while the role of melatonin in the adaptation of the organism to the light-dark cycle of the environment is becoming increasingly recognized. The aim of this study was to investigate the effect of a manipulation of the melatonin rhythm on pituitary hormone secretion in man. DESIGN: Double-blind controlled clinical study. SUBJECTS: Ten adult healthy male volunteers, aged 21-33 years, were studied on two occasions: once after the administration of melatonin 5 mg orally for 4 days at 1700 hours and once after the administration of placebo, at similar times. On the day of each study the subjects undertook their normal duties but refrained from taking heavy exercise, from smoking and drinking alcohol. MEASUREMENTS: Serum cortisol, growth hormone, prolactin and plasma vasopressin, oxytocin, melatonin, sodium, potassium, osmolality and packed cell volume were measured over the following 24 hours. RESULTS: The cortisol peak was advanced and prolactin release increased after melatonin administration, while growth hormone was not affected. Vasopressin and oxytocin levels were found to increase during the night in the control study, but the period of the nocturnal increase in vasopressin concentrations was reduced after the administration of melatonin and the nocturnal increase of oxytocin was absent. CONCLUSION: Altering the melatonin rhythm may affect neuroendocrine function, influencing the nocturnal pattern of neurohypophysial hormone secretion, augmenting prolactin release and advancing the peak of cortisol release

Immunomodulatory effects of aged garlic extract.

Kyo E, Uda N, Kasuga S, et al.

J Nutr. 2001 Mar; 131(3s):1075S-9S.

Using various kinds of models, we examined the effects of aged garlic extract (AGE) on immune functions. In the immunoglobulin (Ig)E-mediated allergic mouse model, AGE significantly decreased the antigen-specific ear swelling induced by picryl chloride ointment to the ear and intravenous administration of antitrinitrophenyl antibody. In the transplanted carcinoma cell model, AGE significantly inhibited the growth of Sarcoma-180 (allogenic) and LL/2 lung carcinoma (syngenic) cells transplanted into mice. Concomitantly, increases in natural killer (NK) and killer activities of spleen cells were observed in Sarcoma-180--bearing mice administered AGE. In the psychological stress model, AGE significantly prevented the decrease in spleen weight and restored the reduction of anti-SRBC hemolytic plaque-forming cells caused by the electrical stress. These studies strongly suggest that AGE could be a promising candidate as an immune modifier, which maintains the homeostasis of immune functions; further studies are warranted to determine when it is most beneficial

[Administration of RU 41740, a preventive anti-infective immunomodulator in an acute respiratory episode. Synthesis of 3 clinical trials].

Lacaille F.

Presse Med. 1988 Jul 27; 17(28):1453-7.

In both adults and children RU 41740 exerts an immunomodulating effect and prevents recurrent respiratory infections. Patients with such infections frequently consult for acute episodes, and it was deemed necessary to evaluate the safety of the drug given concomitantly with antibiotic in acute infections. Three double-blind, drug versus placebo studies were conducted in fragile institutionalized or hospitalized patients. Antibiotics were administered simultaneously with RU 41740 in one group and with a placebo in another group. The studies performed by Albarede and Ollivier showed that in acute respiratory infections RU 41740 was well tolerated and resulted in a more rapid improvement of severity score. Grassi and al. studied chronic bronchitis patients admitted for acute on chronic episode. RU 41740 produced a more rapid improvement in the most severely ill patients, and it was well tolerated. It is concluded that RU 41740 can be initiated safely in acute episodes occurring in subjects with recurrent respiratory infections, and that it results in a faster improvement of clinical symptoms

The relationship between clinical stage, natural killer activity and related immunological parameters in adenocarcinoma of the prostate.

Lahat N, Alexander B, Levin DR, et al.

Cancer Immunol Immunother. 1989; 28(3):208-12.

Several immunological in vitro tests were performed on peripheral blood mononuclear cells of patients with adenocarcinoma of the prostate, stages A, B, C, D. The cytotoxicity of effector natural killer cells towards K-562 targets decreased with increasing disease spread, while their percentage was not significantly changed. The proportion of CD4 (helper/inducer) cells tended to fall with tumor advance, but the proportion of CD8 (suppressor/cytotoxic) cells remained almost constant. Secretion of interleukin-2 from peripheral blood mononuclear cells was diminished with disease progression. Pretreatment of a patient's lymphocytes with cimetidine (antagonist of H-2-bearing suppressor T cells) or indomethacin (inhibitor of prostaglandin synthesis) enhanced natural killer activity. Our data point to the existence of aberrant immune functions in early stages of carcinoma of the prostate and to aggravation of these immune abnormalities in advanced disease

Endocrine and immune effects of melatonin therapy in metastatic cancer patients.

Lissoni P, Barni S, Crispino S, et al.

Eur J Cancer Clin Oncol. 1989 May; 25(5):789-95.

Melatonin, the most important indole hormone produced by the pineal gland, appears to inhibit tumor growth; moreover, altered melatonin secretion has been reported in cancer patients. Despite these data, the possible use of melatonin in human neoplasms remains to be established. The aim of this clinical trial was to evaluate the therapeutic, immunological and endocrine effects of melatonin in patients with metastatic solid tumor, who did not respond to standard therapies. The study was carried out on 14 cancer patients (colon, six; lung, three; pancreas, two; liver, two; stomach, one). Melatonin was given intramuscularly at a daily dose of 20 mg at 3.00 p.m., followed by a maintenance period in an oral dose of 10 mg daily in patients who had a remission, stable disease or an improvement in PS. Before and after the first 2 months of therapy, GH, somatomedin-C, beta-endorphin, melatonin blood levels and lymphocyte subpopulations were evaluated. A partial response was achieved in one case with cancer of the pancreas, with a duration of 18+ months; moreover, six patients had stable disease, while the other eight progressed. An evident improvement in PS was obtained in 8/14 patients. In patients who did not progress, T4/T8 mean ratio was significantly higher after than before melatonin therapy, while it decreased in patients who progressed. On the contrary, hormonal levels were not affected by melatonin administration. This study would suggest that melatonin may be of value in untreatable metastatic cancer patients, particularly in improving their PS and quality of life; moreover, based on its effects on the immune system, melatonin could be tested in association with other antitumor treatments

A randomized study of immunotherapy with low-dose subcutaneous interleukin-2 plus melatonin vs chemotherapy with cisplatin and etoposide as first-line therapy for advanced non-small cell lung cancer.

Lissoni P, Meregalli S, Fossati V, et al.

Tumori. 1994 Dec 31; 80(6):464-7.

AIMS AND BACKGROUND: The therapeutic role of chemotherapy in advanced non-small cell lung cancer (NSCLC) is controversial because of its potentially detrimental action on host anticancer defenses. On the contrary, IL-2 would seem to prolong survival time by improving the immune status, even though it is generally less effective in determining tumor regression in NSCLC. Our previous studies have suggested the possibility of increasing tumor sensitivity to IL-2 by concomitant administration of immunomodulating neurohormones, such as the pineal hormone melatonin (MLT). On this basis, a study was carried out to evaluate the efficacy of immunotherapy with low-dose IL-2 plus MLT versus chemotherapy in advanced NSCLC. METHODS: The study included 60 patients with locally advanced or metastatic NSCLC, who were randomized to receive immunotherapy or chemotherapy. The immunotherapy consisted of IL-2 (3 million IU/day subcutaneously for 6 days/week for 4 weeks) and MLT (40 mg/day orally every day, starting 7 days before IL-2); in nonprogressing patients, a second cycle was repeated after a 21-day rest period, then they underwent a maintenance period consisting of one week of therapy every month until progression. Chemotherapy consisted of cisplatin (20 mg/m2) and etoposide (100 mg/m2)/day intravenously for 3 days; cycles of chemotherapy were repeated every 21 days until progression. RESULTS: No complete response was obtained. A partial response was achieved in 7/29 patients treated with chemotherapy and in 6/31 patients receiving chemotherapy. The difference was not significant. In contrast, the mean progression-free period and the percentage survival at 1 year was significantly higher in patients treated with immunotherapy than in those treated with chemotherapy. Toxicity was substantially lower in patients receiving immunotherapy than in those given chemotherapy. CONCLUSIONS: This randomized study showed that immunotherapy with low-dose IL-2 plus MLT is a better tolerated and more effective therapy in terms of survival time than chemotherapy containing cisplatin in patients affected by advanced NSCLC

A randomized study with the pineal hormone melatonin versus supportive care alone in patients with brain metastases due to solid neoplasms.

Lissoni P, Barni S, Ardizzoia A, et al.

Cancer. 1994 Feb 1; 73(3):699-701.

BACKGROUND. Unresectable brain metastases remain an untreatable disease. Because of its antitumor cytostatic action and its anticonvulsant effect, the pineal hormone melatonin could constitute a new effective agent in the treatment of brain metastases. The current study was performed to evaluate the effect of melatonin on the survival time in patients with brain metastases due to solid neoplasms. METHODS. The study included 50 patients, who were randomized to be treated with supportive care alone (steroids plus anticonvulsant agents) or with supportive care plus melatonin (20 mg/day at 8:00 p.m. orally). RESULTS. The survival at 1 year, free-from-brain-progression period, and mean survival time were significantly higher in patients treated with melatonin than in those who received the supportive care alone. Conversely, steroid-induced metabolic and infective complications were significantly more frequent in patients treated with supportive care alone than in those concomitantly treated with melatonin. CONCLUSIONS. The pineal hormone melatonin may be able to improve the survival time and the quality of life in patients with brain metastases due to solid tumors

Pineal-opioid system interactions in the control of immunoinflammatory responses.

Lissoni P, Barni S, Tancini G, et al.

Ann N Y Acad Sci. 1994 Nov 25; 741:191-6.

Several studies have demonstrated involvement of the pineal gland in the regulation of neuropeptide secretion and activity. In particular, the existence of links between the pineal gland and the brain opioid system has been documented. Both opioid peptides and melatonin (MLT), the most investigated pineal hormone, play an important role in neuromodulation of the immunity. Moreover, the immune effects of MLT are mediated by endogenous opioid peptides, which may be produced by both the endocrine system and the immune cells. In addition, the immune dysfunctions that characterize some human diseases, such as cancer, depend not only on the immune system per se, but also at least in part, on altered secretion of immunomodulating neurohormones, including MLT and opioid peptides. Therefore, the exogenous administration of neurohormones could potentially improve the immune status in humans. The present study evaluates the effects of MLT on changes in the number of T lymphocytes, natural killer cells, and eosinophils induced by exogenous administration of interleukin-2 (IL-2). Macrophage activity was also evaluated by determining serum levels of its specific marker, neopterin. The study was performed in 90 patients with advanced solid neoplasms, who received IL-2 at a dose of 3 million IU/day subcutaneously for 6 days a week for 4 weeks plus MLT at a daily dose of 40 mg. Both drugs were given in the evening. The results were compared to those in 40 cancer patients treated with IL-2 alone. The mean increase in T lymphocytes, natural killer cells, and eosinophils was significantly higher in patients treated with IL-2 plus MLT than in those who received IL-2 alone.(ABSTRACT TRUNCATED AT 250 WORDS)

A randomized study of immunotherapy with low-dose subcutaneous interleukin-2 plus melatonin vs chemotherapy with cisplatin and etoposide as first-line therapy for advanced non-small cell lung cancer.

Lissoni P, Meregalli S, Fossati V, et al.

Tumori. 1994 Dec 31; 80(6):464-7.

AIMS AND BACKGROUND: The therapeutic role of chemotherapy in advanced non-small cell lung cancer (NSCLC) is controversial because of its potentially detrimental action on host anticancer defenses. On the contrary, IL-2 would seem to prolong survival time by improving the immune status, even though it is generally less effective in determining tumor regression in NSCLC. Our previous studies have suggested the possibility of increasing tumor sensitivity to IL-2 by concomitant administration of immunomodulating neurohormones, such as the pineal hormone melatonin (MLT). On this basis, a study was carried out to evaluate the efficacy of immunotherapy with low-dose IL-2 plus MLT versus chemotherapy in advanced NSCLC. METHODS: The study included 60 patients with locally advanced or metastatic NSCLC, who were randomized to receive immunotherapy or chemotherapy. The immunotherapy consisted of IL-2 (3 million IU/day subcutaneously for 6 days/week for 4 weeks) and MLT (40 mg/day orally every day, starting 7 days before IL-2); in nonprogressing patients, a second cycle was repeated after a 21-day rest period, then they underwent a maintenance period consisting of one week of therapy every month until progression. Chemotherapy consisted of cisplatin (20 mg/m2) and etoposide (100 mg/m2)/day intravenously for 3 days; cycles of chemotherapy were repeated every 21 days until progression. RESULTS: No complete response was obtained. A partial response was achieved in 7/29 patients treated with chemotherapy and in 6/31 patients receiving chemotherapy. The difference was not significant. In contrast, the mean progression-free period and the percentage survival at 1 year was significantly higher in patients treated with immunotherapy than in those treated with chemotherapy. Toxicity was substantially lower in patients

receiving immunotherapy than in those given chemotherapy. CONCLUSIONS: This randomized study showed that immunotherapy with low-dose IL-2 plus MLT is a better tolerated and more effective therapy in terms of survival time than chemotherapy containing cisplatin in patients affected by advanced NSCLC

Immune effects of preoperative immunotherapy with high-dose subcutaneous interleukin-2 versus neuroimmunotherapy with low-dose interleukin-2 plus the neurohormone melatonin in gastrointestinal tract tumor patients.

Lissoni P, Brivio F, Brivio O, et al.

J Biol Regul Homeost Agents. 1995 Jan; 9(1):31-3.

Surgery-induced immunosuppression could influence tumor/host interactions in surgically treated cancer patients. Previous studies have shown that high-dose IL-2 preoperative therapy may neutralize surgery-induced lymphocytopenia. Moreover, experimental studies have demonstrated that the immunomodulating neurohormone melatonin (MLT) may amplify IL-2 activity and reduce its dose required to activate the immune system. On this basis, we have compared the immune effects of presurgical therapy with high-dose IL-2 with respect to those obtained with preoperative neuroimmunotherapy consisting of low-dose IL-2 plus MLT. The study included 30 patients with gastrointestinal tract tumors, who were randomized to undergo surgery alone, or surgery plus a preoperative biotherapy with high-dose IL-2 (18 million IU/day subcutaneously for 3 days) or low-dose IL-2 (6 million IU/day subcutaneously for 5 days) plus MLT (40 mg/day orally). Patients underwent surgery within 36 hours from IL-2 interruption. Both IL-2 plus MLT were able to prevent surgery-induced lymphocytopenia. However, mean number of lymphocytes, T lymphocytes and T helper lymphocytes observed on day 1 of postoperative period was significantly higher in patients treated with IL-2 plus MLT than in those receiving IL-2 alone. Moreover, toxicity was less in patients treated with IL-2 and MLT. This biological study shows that both immunotherapy with high-dose IL-2 or neuroimmunotherapy with low-dose IL-2 plus MLT preoperatively are tolerated biotherapies, capable of neutralizing surgery-induced lymphocytopenia in cancer patients. Moreover, the study would suggest that the neuroimmunotherapy may induce a more rapid effect on postoperative immune changes with respect to IL-2 alone

The immunoneuroendocrine role of melatonin.

Maestroni GJ.

J Pineal Res. 1993 Jan; 14(1):1-10.

A tight, physiological link between the pineal gland and the immune system is emerging from a series of experimental studies. This link might reflect the evolutionary connection between self-recognition and reproduction. Pinealectomy or other experimental methods which inhibit melatonin synthesis and secretion induce a state of immunodepression which is counteracted by melatonin. In general, melatonin seems to have an immunoenhancing effect that is particularly apparent in immunodepressive states. The negative effect of acute stress or immunosuppressive pharmacological treatments on various immune parameters are counteracted by melatonin. It seems important to note that one of the main targets of melatonin is the thymus, i.e., the central organ of the immune system. The clinical use of melatonin as an immunotherapeutic agent seems promising in primary and secondary immunodeficiencies as well as in cancer immunotherapy. The immunoenhancing action of melatonin seems to be mediated by T-helper cell-derived opioid peptides as well as by lymphokines and, perhaps, by pituitary hormones. Melatonin-induced-immuno-opioids (MIIO) and lymphokines imply the presence of specific binding sites or melatonin receptors on cells of the immune system. On the other hand, lymphokines such as gamma-interferon and interleukin-2 as well as thymic hormones can modulate the synthesis of melatonin in the pineal gland. The pineal gland might thus be viewed as the crux of a sophisticated immunoneuroendocrine network which functions as an unconscious, diffuse sensory organ

Inhibition of human immunodeficiency virus type-1 integrase by curcumin.

Mazumder A, Raghavan K, Weinstein J, et al.

Biochem Pharmacol. 1995 Apr 18; 49(8):1165-70.

Curcumin (diferuloylmethane) is the yellow pigment in turmeric (Curcuma longa L.) that is widely used as a spice, food coloring (curry) and preservative. Curcumin exhibits a variety of pharmacological effects including antitumor, anti-inflammatory, and anti-infectious activities and is currently in clinical trials for AIDS patients. The effects of curcumin have been determined on purified human immunodeficiency virus type 1 (HIV-1) integrase. Curcumin has an inhibitory concentration50 (IC50) for strand transfer of 40 microM. Inhibition of an integrase deletion mutant containing only amino acids 50-212 suggests that curcumin interacts with the integrase catalytic core. Two structural analogs, methyl cinnamate and chlorogenic acid, were inactive. Energy minimization studies suggest that the anti-integrase activity of curcumin could be due to an intramolecular stacking of two phenyl rings that brings the hydroxyl groups into close proximity. The present data suggest that HIV-1 integrase inhibition may contribute to the antiviral activity of curcumin. These observations suggest new strategies for antiviral drug development that could be based upon

curcumin as a lead compound for the development of inhibitors of HIV-1 integrase

Oseltamivir: a review of its use in influenza.

McClellan K, Perry CM.

Drugs. 2001; 61(2):263-83.

Oseltamivir is a prodrug of oseltamivir carboxylate (Ro 64-0802, GS4071), a potent and selective inhibitor of the neuraminidase glycoprotein essential for replication of influenza A and B viruses. Studies in volunteers with experimental human influenza A or B showed that administration of oral oseltamivir 20 to 200 mg twice daily for 5 days reduced both the quantity and duration of viral shedding compared with placebo. Subsequent assessment of the drug at a dosage of 75 mg twice daily for 5 days in otherwise healthy adults with naturally acquired febrile influenza showed that oseltamivir reduced the duration of the disease by up to 1.5 days and the severity of illness by up to 38% compared with placebo when initiated within 36 hours of symptom onset (earlier initiation of therapy was associated with faster resolution). The incidence of secondary complications and the use of antibacterials were also reduced significantly in oseltamivir recipients. A liquid formulation of oseltamivir (2 mg/kg twice daily for 5 days) has been shown to be effective in the treatment of children with influenza, and data presented in abstracts suggest that the drug may also be of use in high-risk populations such as the elderly or those with chronic cardiac or respiratory disease. In addition to treatment efficacy, the drug has demonstrated efficacy when used for seasonal or household prophylaxis. Oral oseltamivir (75 mg once or twice daily for 6 weeks) during a period of local influenza activity significantly prevented the development of naturally acquired influenza by >70% compared with placebo in unvaccinated otherwise healthy adults. The drug also demonstrated efficacy when used adjunctively in previously vaccinated high-risk elderly patients (92% protective efficacy). Short term administration of oseltamivir (75 mg once daily for 7 days) may significantly reduce the risk of illness in household contacts of infected persons when administered within 48 hours of symptom onset in the infected person. Oseltamivir 75 mg twice daily for 5 days was well tolerated in clinical trials in healthy adults and high-risk patients, with nausea and vomiting being the most commonly reported events. Gastrointestinal events were mild and transient and both nausea and vomiting were less likely when oseltamivir was taken with food. Conclusions: Oseltamivir is a well tolerated orally active neuraminidase inhibitor which significantly reduces the duration of symptomatic illness and hastens the return to normal levels of activity when initiated promptly in patients with naturally acquired influenza. It therefore represents a useful therapeutic alternative to zanamivir (especially in patients who prefer oral administration or who have an underlying respiratory disorder) and the M2 inhibitors amantadine and rimantadine (because of its broader spectrum of anti-influenza activity and lower likelihood of resistance) in patients with influenza. In addition, although annual vaccination remains the best means of influenza prevention, there may be a place for oseltamivir in providing household prophylaxis or adjunctive prophylaxis in high-risk vaccinated patients during an outbreak of the disease or for use in patients in whom vaccination is unsuitable or ineffective

Virological and immunological effects of antioxidant treatment in patients with HIV infection.

Muller F, Svardal AM, Nordoy I, et al.

Eur J Clin Invest. 2000 Oct; 30(10):905-14.

BACKGROUND: Intracellular oxidative stress in CD4+ lymphocytes due to disturbed glutathione homeostasis may lead to impaired lymphocyte functions and enhanced HIV replication in patients with HIV infection, especially in those with advanced immunodeficiency. The aim of the present study was to assess whether short-term, high-dose antioxidant treatment might have effects on immunological and virological parameters in patients with HIV infection. MATERIALS AND METHODS: In this pilot study, we examined virological and immunological effects of antioxidant combination treatment for 6 days with high doses of N-acetylcysteine (NAC) and vitamin C in 8 patients with HIV infection. The following were assayed before, during and after antioxidant treatment: HIV RNA plasma levels; numbers of CD4+, CD8+, and CD14+ leukocytes in blood; plasma thiols; intracellular glutathione redox status in CD4+ lymphocytes and CD14+ monocytes; lymphocyte proliferation; lymphocyte apoptosis and plasma levels of tumour necrosis factor (TNF)alpha; soluble TNF receptors and neopterin in plasma. RESULTS: No significant changes in HIV RNA plasma levels or CD4+ lymphocyte counts in blood were noted during antioxidant treatment in the patient group. However, in the 5 patients with the most advanced immunodeficiency (CD4+ lymphocyte counts < 200 x 106 L(-1)), a significant rise in CD4+ lymphocyte count, a reduction in HIV RNA plasma level of 0.8 log, an enhanced lymphocyte proliferation and an increased level of intracellular glutathione in CD4+ lymphocytes were found. No change in lymphocyte apoptosis was noted. CONCLUSIONS: Short-term, high-dose combination treatment with NAC and vitamin C in patients with HIV infection and advanced immunodeficiency lead to immunological and virological effects that might be of therapeutic value

Inhalation of interleukin-2 combined with subcutaneous administration of interferon for the treatment of pulmonary metastases from renal cell carcinoma.

Nakamoto T, Kasaoka Y, Mitani S, et al.

Int J Urol. 1997 Jul; 4(4):343-8.

BACKGROUND: Interleukin-2 is the most promising antitumor agent for advanced renal cell carcinoma, but systemic immunotherapy with interleukin-2 might be limited because of inadequate efficacy and severe adverse effects. In this study, we treated 7 patients with lung metastases from renal cell carcinoma with topical application of interleukin-2 by inhalation. METHODS: Patients received 100,000 IU of interleukin-2 by inhalation 4 times a day and 9,000,000 IU of interferon-alfa-2a subcutaneously for 5 consecutive days per week. They also received, by oral administration, 800 mg of cimetidine and 50 mg of indomethacin per day. After informed consent was obtained, the treatment started and the absence of any intolerable adverse effects was confirmed in a hospital. Then the treatment continued in an outpatient clinic for at least 3 months. RESULTS: Of 6 assessable patients, 5 responded to this treatment; 2 patients developed a partial response (33%) and 3 remained stable (67%). Disease progressed in the remaining patient. Therapy was discontinued in 1 patient because of his poor general condition. No severe adverse effects were observed, but pulmonary fibrosis probably associated with this treatment occurred in 1 patient. CONCLUSION: Although more cases and further evaluation are necessary to assess the significance and the safety of the inhalation of interleukin-2, this treatment is anticipated to be an option for selected patients with lung metastases from renal cell carcinoma

Use of echinacea in medicine.

Percival SS.

Biochem Pharmacol. 2000 Jul 15; 60(2):155-8.

Echinacea, also known as the purple coneflower, is an herbal medicine that has been used for centuries, customarily as a treatment for the common cold, coughs, bronchitis, upper respiratory infections, and some inflammatory conditions. Research on echinacea, including clinical trials, is limited and largely in German. More information is needed before a definitive statement about the efficacy of echinacea can be made. Future work needs to clearly identify the species of echinacea and distinguish between the efficacy of the different plant parts (roots versus upper plant parts). Although many of the active compounds of echinacea have been identified, the mechanism of action is not known, nor is the bioavailability, relative potency, or synergistic effects of the active compounds known. Interpretation of existing literature suggests that echinacea should be used as a treatment for illness, not as a means for prevention of illness. The consensus of the studies reviewed in this article is that echinacea is indeed effective in reducing the duration and severity of symptoms, but that this effect is noted only with certain preparations of echinacea. Studies show that the plant and its active components affect the phagocytic immune system, but not the specifically acquired immune system

Long-term use of oseltamivir for the prophylaxis of influenza in a vaccinated frail older population.

Peters PH, Jr., Gravenstein S, Norwood P, et al.

J Am Geriatr Soc. 2001 Aug; 49(8):1025-31.

OBJECTIVES: To investigate the efficacy of once-daily oral oseltamivir for 6 weeks (Tamiflu) in prophylaxis against laboratory-confirmed clinical influenza in frail older subjects living in homes for seniors and to determine the safety and tolerability of long-term oseltamivir. DESIGN: Double-blind, placebo-controlled, parallel-group, randomized, multicenter study. SETTING: Thirty-one residential homes for seniors across United States and Europe. PARTICIPANTS: Five hundred forty-eight frail older occupants (mean age 81 years, >80% vaccinated). INTERVENTION: Prophylaxis with oseltamivir 75 mg or placebo once daily for 6 weeks, beginning when influenza was detected locally. MEASUREMENTS: The primary efficacy endpoint was laboratory-confirmed clinical influenza. RESULTS: Oseltamivir administration resulted in a 92% reduction in the incidence of laboratory-confirmed clinical influenza compared with placebo (placebo 12/272 (4.4%), oseltamivir 1/276 (0.4%); P = .002). Of subjects vaccinated against influenza, oseltamivir was 91% effective in preventing laboratory-confirmed clinical influenza (placebo 11/218 (5.0%), oseltamivir 1/222 (0.5%); P = .003). Oseltamivir use was associated with a significant reduction in the incidence of secondary complications (placebo 7/272 (2.6%), oseltamivir 1/276 (0.4%); P = .037). Although nearly all subjects were taking concomitant medication both before and during the study, oseltamivir was well tolerated. A similar incidence of adverse events, including gastrointestinal effects, occurred in both groups. There was no suppression of antibody response in oseltamivir recipients. CONCLUSION: Oral oseltamivir 75 mg once daily for 6 weeks effectively prevented clinical influenza in vaccinated frail older subjects using significant concomitant medications in a residential care setting. The treatment was well tolerated and provided additional protection to that afforded by vaccination

[Chronic bronchitis. Value of RU 41740].

Piquet J, Bignon J.

Presse Med. 1988 Jul 27; 17(28):1441-4.

Chronic bronchitis is responsible for 20,000 deaths per annum in France, i.e. 5 per cent of the overall mortality rate. Infection of the bronchi and lung tissue is a frequent cause of death in these patients. Acute on chronic bronchitis ranks fifth among the causes of disablement and admission to hospital. Pneumococci and Haemophilus influenza are the organisms most frequently isolated. the incidence and potential severity of acute episodes of infection account for the repeated use of antibiotics which carries a risk of promotion bacterial resistance. RU 41740 is a non-specific immunomodulator agent which reinforces the non-specific means of the respiratory tract against infections. Three double-blind, drug versus placebo and therefore reliable therapeutic trials have shown that the drug is effective in preventing airway infection. In patients with moderately advanced chronic bronchitis, RU 41740 reduces the number and duration of acute infectious episodes as well as antibiotic consumption. This positive effect persists in patients with chronic respiratory failure, including those who present with extensive bronchial dystrophy. RU 41740 is particularly effective in patients with numerous previous episodes of infection, but it also acts at all stages of chronic bronchitis

Increase in the number and the phagocytic function of guinea pig pulmonary and peritoneal macrophages following oral administration of RU 41740, a glycoprotein extract from Klebsiella pneumoniae.

Radermecker M, Rommain M, Maldague MP, et al.

Int J Immunopharmacol. 1988; 10(8):913-7.

RU 41740 (Biostim) which is a purified glycoprotein extract from Klebsiella pneumoniae, is an orally active non-specific immunostimulant. In guinea pigs, 8 days after a 7 days oral administration of RU 41740 (10 or 100 mg/kg/day), an increase in the cell population of the pulmonary and peritoneal cavities was observed, especially in that of the macrophages. RU 41740 also enhanced the phagocytic activity of both the alveolar and peritoneal macrophages, when their chemotactic activity was not significantly modified. This increase in the number of pulmonary macrophages and the stimulation of their phagocytic function might explain the protective effect afforded by the oral administration of Biostim against respiratory infections in patients with chronic bronchitis

Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial. US Oral Neuraminidase Study Group.

Treanor JJ, Hayden FG, Vrooman PS, et al.

JAMA. 2000 Feb 23; 283(8):1016-24.

CONTEXT: Previous studies have shown oseltamivir, a neuraminidase inhibitor, to be effective in preventing influenza and treating experimental influenza. OBJECTIVE: To evaluate the efficacy and safety of oseltamivir in the treatment of naturally acquired influenza infection. DESIGN: Randomized, placebo-controlled, double-blind study conducted January through March 1998. SETTING: Sixty primary care and university health centers throughout the United States. PARTICIPANTS: A total of 629 healthy nonimmunized adults aged 18 to 65 years with febrile respiratory illness of no more than 36 hours' duration with temperature of 38 degrees C or more plus at least 1 respiratory symptom and 1 constitutional symptom. INTERVENTIONS: Individuals were randomized to 1 of 3 treatment groups with identical appearing pills: oral oseltamivir phosphate, 75 mg twice daily (n = 211) or 150 mg (n = 209) twice daily, or placebo (n = 209). MAIN OUTCOME MEASURES: Duration and severity of illness in individuals infected with influenza. RESULTS: Two individuals withdrew before receiving medication and were excluded from further analyses. A total of 374 individuals (59.6%) were infected with influenza. Their duration of illness was reduced by more than 30% with both oseltamivir, 75 mg twice daily (median, 71.5 hours; P < .001), and oseltamivir, 150 mg twice daily (median, 69.9 hours; P = ".006)," compared with placebo (median, 103.3 hours). Severity of illness was reduced by 38% (median score, 597 score-hours; P < .001) with oseltamivir, 75 mg twice daily, and by 35% (median score, 626 score-hours; P < .001) with oseltamivir, 150 mg twice daily, vs placebo (median score, 963 score-hours). Oseltamivir treatment reduced the duration of fever and oseltamivir recipients returned to usual activities 2 to 3 days earlier than placebo recipients (P < or = ".05)." Secondary complications such as bronchitis and sinusitis occurred in 15% of placebo recipients compared with 7% of combined oseltamivir recipients (P = ".03)." Among all 629 subjects, oseltamivir reduced illness duration (76.3 hours and 74.3 hours for 75 mg and 150 mg, respectively, vs 97.0 hours for placebo; P = ".004" for both comparisons) and illness severity (686 score-hours and 629 score-hours for 75 mg and 150 mg, respectively, vs 887 score-hours for placebo; P < .001 for both comparisons). Nausea and vomiting occurred more frequently in both oseltamivir groups (combined, 18.0% and 14.1%, respectively; P = ".002)" than in the placebo group (7.4% and 3.4%; P < .001). CONCLUSIONS: Our data suggest that oral oseltamivir treatment reduces the duration and severity of acute influenza in healthy adults and may decrease the incidence of secondary complications

[Double-blind study of an immunomodulator of bacterial origin (Biostim) in the prevention of infectious episodes in chronic bronchitis].

Viallat JR, Costantini D, Boutin C, et al.

Poumon Coeur. 1983 Jan; 39(1):53-7.

A double-blind trial was conducted to evaluate the capacity of an immunomodulator of bacterial origin (Biostim) to diminish the frequency of infectious episodes in chronic bronchitis. The study duration was 9 months, Biostim being administered orally initially, with follow-up examinations after 2 and 4 months. Of the 73 subjects selected, 38 received Biostim and 35 a placebo (no significant differences between the two groups). By the 9th month, the duration in days of infectious episodes and of antibiotic therapy was 13 +/- 1.3 and 11.5 +/- 1.4 days respectively for the group receiving Biostim, and 33 +/- 5.8 and 41 +/- 9.5 respectively for the placebo group (p less than 0.05). No signs of intolerance and particularly no immunotoxicity were observed: absence of elevation of IgE or anti-Biostim antibody titres. Pre-winter administration of Biostim to subjects at high risk would appear to significantly diminish the frequency of infectious episodes and thus the consumption of antibiotics

Effectiveness of oseltamivir in preventing influenza in household contacts: a randomized controlled trial.

Welliver R, Monto AS, Carewicz O, et al.

JAMA. 2001 Feb 14; 285(6):748-54.

CONTEXT: Influenza virus is easily spread among the household contacts of an infected person, and prevention of influenza in household contacts can control spread of influenza in the community. OBJECTIVE: To investigate the efficacy of oseltamivir in preventing spread of influenza to household contacts of influenza-infected index cases (ICs). DESIGN AND SETTING: Randomized, double-blind, placebo-controlled study conducted at 76 centers in North America and Europe during the winter of 1998-1999. PARTICIPANTS: Three hundred seventy-seven ICs, 163 (43%) of whom had laboratory-confirmed influenza infection, and 955 household contacts (aged >/=12 years) of all ICs (415 contacts of influenza-positive ICs). INTERVENTIONS: Household contacts were randomly assigned by household cluster to take 75 mg of oseltamivir (n = 493) or placebo (n = 462) once daily for 7 days within 48 hours of symptom onset in the IC. The ICs did not receive antiviral treatment. MAIN OUTCOME MEASURE: Clinical influenza in contacts of influenza-positive ICs, confirmed in a laboratory by detection of virus shedding in nose and throat swabs or a 4-fold or greater increase in influenza-specific serum antibody titer between baseline and convalescent serum samples. RESULTS: In contacts of an influenza-positive IC, the overall protective efficacy of oseltamivir against clinical influenza was 89% for individuals (95% confidence interval [CI], 67%-97%; P<.001) and 84% for households (95% CI, 49%-95%; P<.001). In contacts of all ICs, oseltamivir also significantly reduced incidence of clinical influenza, with 89% protective efficacy (95% CI, 71%-96%; P<.001). Viral shedding was inhibited in contacts taking oseltamivir, with 84% protective efficacy (95% CI, 57%-95%; P<.001). All virus isolates from oseltamivir recipients retained sensitivity to the active metabolite. Oseltamivir was well tolerated; gastrointestinal tract effects were reported with similar frequency in oseltamivir (9.3%) and placebo (7.2%) recipients. CONCLUSION: In our sample, postexposure prophylaxis with oseltamivir, 75 mg once daily for 7 days, protected close contacts of influenza-infected persons against influenza illness, prevented outbreaks within households, and was well tolerated

Oral oseltamivir treatment of influenza in children.

Whitley RJ, Hayden FG, Reisinger KS, et al.

Pediatr Infect Dis J. 2001 Feb; 20(2):127-33.

BACKGROUND: Oral oseltamivir administration is effective treatment for influenza in adults. This study was conducted to determine the efficacy, safety and tolerability of oseltamivir in children with influenza. METHODS: In this randomized, double blind, placebo-controlled study, children 1 through 12 years with fever [> or =100 degrees F (> or =38 degrees C)] and a history of cough or coryza <48 h duration received oseltamivir 2 mg/kg/dose or placebo twice daily for 5 days. The primary efficacy endpoint was the time to resolution of illness including mild/absent cough and coryza mild/absent, return to normal activity and euthermia. RESULTS: Of 695 enrolled children 452 (65%) had influenza (placebo, n = "235;" oseltamivir, n = "217)." Among infected children the median duration of illness was reduced by 36 h (26%) in oseltamivir compared with placebo recipients (101 h; 95% confidence interval, 89 to 118 vs. 137 h; 95% confidence interval, 125 to 150; P < 0.0001). Oseltamivir treatment also reduced cough, coryza and duration of fever. New diagnoses of otitis media were reduced by 44% (12% vs. 21%). The incidence of physician-prescribed antibiotics was significantly lower in influenza-infected oseltamivir (68 of 217, 31%) than placebo (97 of 235, 41%; P = "0.03)" recipients. Oseltamivir therapy was generally well-tolerated, although associated with an excess frequency of emesis (5.8%). Discontinuation because of adverse events was low in both groups (1.8% with oseltamivir vs. 1.1% with placebo). Oseltamivir treatment did not affect the influenza-specific antibody response. CONCLUSIONS: Oral oseltamivir administration is an efficacious and well-tolerated therapy for influenza in children when given within 48 h of onset of illness

Inhibition of several strains of influenza virus in vitro and reduction of symptoms by an elderberry extract (Sambucus nigra L.) during an outbreak of influenza B Panama.

Zakay-Rones Z, Varsano N, Zlotnik M, et al.

J Altern Complement Med. 1995; 1(4):361-9.

A standardized elderberry extract, Sambucol (SAM), reduced hemagglutination and inhibited replication of human influenza viruses type A/Shangdong 9/93 (H3N2), A/Beijing 32/92 (H3N2), A/Texas 36/91 (H1N1), A/Singapore 6/86 (H1N1), type B/Panama 45/90, B/Yamagata 16/88, B/Ann Arbor 1/86, and of animal strains from Northern European swine and turkeys, A/Sw/Ger 2/81, A/Tur/Ger 3/91, and A/Sw/Ger 8533/91 in Madin-Darby canine kidney cells. A placebo-controlled, double blind study was carried out on a group of individuals living in an agricultural community (kibbutz) during an outbreak of influenza B/Panama in 1993. Fever, feeling of improvement, and complete cure were recorded during 6 days. Sera obtained in the acute and convalescent phases were tested for the presence of antibodies to influenza A, B, respiratory syncytial, and adenoviruses. Convalescent phase serologies showed higher mean and mean geometric hemagglutination inhibition (HI) titers to influenza B in the group treated with SAM than in the control group. A significant improvement of the symptoms, including fever, was seen in 93.3% of the cases in the SAM-treated group within 2 days, whereas in the control group 91.7% of the patients showed an improvement within 6 days ($p < 0.001$). A complete cure was achieved within 2 to 3 days in nearly 90% of the SAM-treated group and within at least 6 days in the placebo group ($p < 0.001$). No satisfactory medication to cure influenza type A and B is available. Considering the efficacy of the extract in vitro on all strains of influenza virus tested, the clinical results, its low cost, and absence of side-effects, this preparation could offer a possibility for safe treatment for influenza A and B

[Protective effect of tea on immune function in mice].

Zhu M, Gong Y, Yang Z.

Zhonghua Yu Fang Yi Xue Za Zhi. 1998 Sep; 32(5):270-4.

OBJECTIVE: To study the mechanism of preventive effect of tea on cancer by immune regulation. METHODS: A tumor model was induced in mice using carcinogen, 4-methyl-nitrosoamino-1-(3-pyridyl)-1-butanone (NNK), to examine their changes in immune function and the effects of green tea, mixed tea and polyphenol on protection from tumor. RESULTS: During the four weeks of observation after injection of NNK into mice, their immunological indicators, such as cytophagocytosis of macrophage in the abdominal cavity, chemiluminescence of peripheral leukocyte, delayed allergic reaction, count of antibody-forming spleen cells and activity of spleen nature killer cells, etc. increased or decreased to various extent, as compared with those in normal controls. It was found that whether green tea, mixed tea or polyphenol all showed significant protection from adverse changes in immune functions. CONCLUSION: Tea and its components had significant protection from early adverse changes in immune function in tumorgenesis induced by NNK