19. Influenza Virus (Flu)

Preventative and curative options include:

Echinacea , sambucol, DHEA, multi nutrients, garlic, lactoferrin , alpha-lipoic acid, green tea, vitamin C, whey protein, curcumin, melatonin.

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. Immunology Laboratory for Tumor Diagnosis, Department of Oncology, Hadassah University Hospital, Jerusalem, Israel.

Eur Cytokine Netw 2001 Apr-Jun;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; Maestroni GJ; Pang SF; Reiter RJ; Viswanathan M; Zisapel N Department of Zoology, University of Guelph, Ont., Canada. gbubenik@uoguelph.ca

Biol Signals Recept (Switzerland) Jul-Aug 1998, 7 (4) p195-219

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. Memorial University of Newfoundland.

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. Department of Anatomy and Cell Biology, McGill University, H3A 2B2, Montreal, Canada.

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, Roth E. Department of Surgery, University of Vienna, Austria.

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.

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

Girodon F, Galan P, Monget AL, Boutron-Ruault MC, Brunet-Lecomte P, Preziosi P, Arnaud J, Manuguerra JC, Herchberg S. Scientific and Technical Institute for Foods and Nutrition, Conservatiore National des Arts et Mettiers, Paris, France.

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.

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

Girodon F, Lombard M, Galan P, Brunet-Lecomte P, Monget AL, Arnaud J, Preziosi P, Hercberg S. Institut Scientifique et Technique de la Nutrition et de l'Alimentation, Paris, France.

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.

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 mega dose 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, Lloyd D. Microbiology Group, School of Biosciences, University of Wales, Cardiff, UK.

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.

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

Kang BY, Song YJ, Kim KM, Choe YK, Hwang SY, Kim TS. College of Pharmacy, Chonnam National University, Kwangju 500-757, South Korea.

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, D.F., Wheeler, M.J., Forsling, M.L. Department of Gynaecology, St. Thomas' Hospital, UMDS, London, UK.

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, Itakura Y. Healthcare Research Institute, Wakunaga Pharmaceutical Company, Ltd., Koda-cho, Takata-gun, Hiroshima 739-1195, Japan.

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.

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

Lissoni P, Barni S, Crispino S, Tancini G, Fraschini F. Divisione di Radioterapia Oncologica, Ospedale San Gerardo, Milano, Italy.

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

Lissoni P, Barni S, Ardizzoia A, Tancini G, Conti A, Maestroni G. Division of Radiotherapy, San Gerardo Hospital, Milan, Italy.

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, Fossati V, Frigerio F. Division of Radiation Oncology, San Gerardo Hospital, Monza, Milan, Italy.

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, Paolorossi F, Barni S, Tancini G, Frigerio F. Divisione di Radioterapia Oncologica, Ospedale San Gerardo, Monza, Milano, Italia.

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; Fumagalli L; Gramazio F; Rossi M

J Biol Regul Homeost Agents (Italy) Jan-Mar 1995, 9 (1) p31-3

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 surgeryinduced lymphocytopnia 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 (DENMARK) Jan 1993, 14 (1) p1-10

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, Kohn KW, Pommier Y. Laboratory of Molecular Pharmacology, National Cancer Institute, Bethesda, MD 20892-4255, USA.

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.

Oral supplementation with whey proteins increases plasma glutathione levels of HIV-infected patients.

Micke P, Beeh KM, Schlaak JF, Buhl R. Pulmonary Division, III. Medical Department, Mainz University Hospital, D-455101 Mainz, Germany.

Eur J Clin Invest 2001 Feb;31(2):171-8

HIV infection is characterized by an enhanced oxidant burden and a systemic deficiency of the tripeptide glutathione (GSH), a major antioxidant. The semi-essential amino acid cysteine is the main source of the free sulfhydryl group of GSH and limits its synthesis. Therefore, different strategies to supplement cysteine supply have been suggested to increase glutathione levels in HIV-infected individuals. The aim of this study was to evaluate the effect of oral supplementation with two different cysteine-rich whey protein formulas on plasma GSH levels and parameters of oxidative stress and immune status in HIV-infected patients. In a prospective double blind clinical trial, 30 patients (25 male, 5 female; mean age (+/- SD) 42 +/- 9.8 years) with stable HIV infection (221 +/- 102 CD4 + lymphocytes L-1) were randomized to a supplemental diet with a daily dose of 45 g whey proteins of either Protectamin (Fresenius Kabi, Bad Hamburg, Germany) or Immunocal (Immunotec, Vandreuil, Canada) for two weeks. Plasma concentrations of total, reduced and oxidized GSH, superoxide anion (O2-) release by blood mononuclear cells, plasma levels of TNF-alpha and interleukins 2 and 12 were quantified with standard methods at baseline and after therapy. Pre-therapy, plasma GSH levels (Protectamin: 1.92 +/- 0.6 microM; Immunocal: 1.98 +/- 0.9 microM) were less than normal (2.64 +/- 0.7 microM, P = 0.03). Following two weeks of oral supplementation with whey proteins, plasma GSH levels increased in the Protectamin group by 44 +/- 56% (2.79 +/- 1.2 microM, P = 0.004) while the difference in the Immunocal group did not reach significance (+ 24.5 +/- 59%, 2.51 +/- 1.48 microM, P = 0.43). Spontaneous O2-release by blood mononuclear cells was stable (20.1 +/- 14.2 vs. 22.6 +/- 16.1 nmol h-1 10-6 cells, P = 0.52) whereas PMA-induced O2- release decreased in the Protectamin group (53.7 +/- 19 vs. 39.8 +/- 18 nmol h-1 10-6 cells, P = 0.04). Plasma concentrations of TNF-alpha and interleukins 2 and 12 (P > 0.08, all

comparisons) as well as routine clinical parameters remained unchanged. Therapy was well tolerated. In glutathione-deficient patients with advanced HIV-infection, short-term oral supplementation with whey proteins increases plasma glutathione levels. A long-term clinical trial is clearly warranted to see if this "biochemical efficacy" of whey proteins translates into a more favourable course of the disease.

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

Muller F, Svardal AM, Nordoy I, Berge RK, Aukrust P, Froland SS. University of Oslo, The National Hospital, Rikshospitalet, Oslo, Norway.

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.

Use of echinacea in medicine.

Percival SS. Food Science and Human Nutrition Department, The University of Florida, Gainesville, FL 32611, USA.

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 argely 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 his 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.

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, Manor O, Regev L, Schlesinger M, Mumcuoglu M. Department of Virology, Hebrew University-Hadassah Medical School, Jerusalem, Israel.

J Altern Complement Med 1995 Winter;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. Institute of Radiation Medicine, Academy of Military Medical Sciences, Beijing.

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.

Lactoferrin immunomodulation of DTH response in mice.

Zimecki M, Hunter RL Jr, Kruzel ML. Department of Pathology and Laboratory Medicine-Program in Molecular Pathology, University of Texas-Houston Medical School, UTHHSC, 77030, USA.

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. 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.

20. Migraine

Preventative and curative options include:

Feverfew extract, magnesium, riboflavin, co-enzyme Q10, B-complex vitamins, glucosamine, ginkgo, picamilon, butterbur root, melatonin.

Visual evoked potentials and serum magnesium levels in juvenile migraine patients.

Aloisi P; Marrelli A; Porto C; Tozzi E; Cerone G Servizio di Neurofisiopatologia, University of L'Aquila, Italy.

Headache (United States) Jun 1997, 37 (6) p383-5

Changes in visual evoked potentials and decreased intracellular magnesium levels have been separately described in patients affected by migraine both during the attacks and in the interictal periods. An inverse correlation between increased P100 amplitude and lowered serum magnesium levels was found in children suffering from migraine with and without aura in a headache-free period. A 20-day treatment with oral magnesium pidolate seemed to normalize the magnesium balance in 90% of patients. After treatment, the reduced P100 amplitude confirmed the inverse correlation with the serum magnesium level. These data seem to suggest the hypothesis that higher visual evoked potential amplitude and low brain magnesium level can both be an expression of neuronal hyperexcitability of the visual pathways related to a lowered threshold for migraine attacks.

Nocturnal plasma melatonin profile and melatonin kinetics during infusion in status migrainosus

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Cephalalgia (Norway), 1997, 17/4 (511-517)

The plasma melatonin profile was significantly disturbed (phase-shift of the maximum melatonin level) in four out of six female sufferers from status migrainosus, compared with nine healthy controls. The number of secretion peaks was similar in both groups. A nocturnal 20 pg melatonin infusion (from 21.00 to 01.00 h) evoked plasma melatonin levels slightly higher than a physiological secretion peak. During infusion, the episodes of secretion were reinforced and the endogenous plasma profile was phase-advanced in two patients displaying a phase-delay. These data suggest impaired pineal function in migraine. In the absence of side effects of melatonin infusion, the relief of certain migraine

symptoms described by our patients might support a controlled trial of melatonin in migraine.

An extract of Petasites hybridus is effective in the prophylaxis of migraine.

Grossman W, Schmidramsl H. Department of Neurology, Municipal Hospital, Munchen-Harlaching, Germany.

Altern Med Rev 2001 Jun;6(3):303-10

OBJECTIVE: Migraine is still an unsolved problem. This clinical trial investigates the efficacy and tolerance of Petasites hybridus in the prophylaxis of migraine.

METHODS: A randomized, group-parallel, placebo-controlled, double-blind clinical study was carried out with a special CO2 extract from the rhizome of Petasites hybridus. Following a four-week run-in phase, 60 patients received either the special Petasites hybridus extract Petadolex or placebo at a dosage of two capsules (each capsule contains 25 mg) twice daily over 12 weeks. Outcome variables included the frequency, intensity and duration of migraine attacks as well as any accompanying symptoms.

RESULTS: The frequency of migraine attacks decreased by a maximum of 60 percent compared to the baseline. This reduction in migraine attacks with Petadolex was significant ($p < 0.05$) compared to placebo. No adverse events were reported. Petasites was exceptionally well tolerated.

CONCLUSIONS: The results suggest that migraine patients can benefit from prophylactic treatment with this special extract. The combination of high efficacy and excellent tolerance emphasizes the particular value that Petasites hybridus has for the prophylactic treatment of migraine.

The results of pycamilon therapy in patients with hemicrania.

O A Kolosova, V I Osipova, T V Luniova, All-Union Center of Vegetative Pathology of the Ministry of Health of USSR, First Medical Institute, 11, Rossolimo St., Moscow 119021, USSR

Efficiency of pycamilon in patients with hemicrania was studied. Indications for pycamilon application in response to the clinical form of hemicrania and to the course of disease were defined more exactly. It was been established that pycamilon has a pronounced effect on painful hemicrania access both decreasing its intensity and mitigating or absolute ceasing of accompanying symptoms. Pycamilon is most effective for simple forms of hemicrania with preferential left sided topoalgia in patients without pronounced depressive hypochondria.

Role of magnesium in the pathogenesis and treatment of migraines.

Mauskop A, Altura BM NY Headache Center, New York, NY 10021, USA.

Clin Neurosci 1998;5(1):24-7

The importance of magnesium in the pathogenesis of migraine headaches is clearly established by a large number of clinical and experimental studies. However, the precise role of various effects of low magnesium levels in the development of migraines remains to be discovered. Magnesium concentration has an effect on serotonin receptors, nitric oxide synthesis and release, NMDA receptors, and a variety of other migraine related receptors and neurotransmitters. The available evidence suggests that up to 50% of patients during an acute migraine attack have lowered levels of ionized magnesium. Infusion of magnesium results in a rapid and sustained relief of an acute migraine in such patients. Two double-blind studies suggest that chronic oral magnesium supplementation may also reduce the frequency of migraine headaches. Because of an excellent safety profile and low cost and despite the lack of definitive studies, we feel that a trial of oral magnesium supplementation can be recommended to a majority of migraine sufferers. Refractory patients can sometimes benefit from intravenous infusions of magnesium sulfate.

[The new cerebrovascular preparation pikamilon]

Mirzoian RS; Gan'shina TS

Farmakol Toksikol (USSR) Jan Feb 1989, 52 (1) p23 6,

Picamilon, a sodium salt of N nicotinoyl gamma aminobutyric acid, was shown to induce a significant increase of cerebral blood flow in conscious cats. Picamilon was found to inhibit neurogenic spasms of cerebral vessels that was followed by suppression of tonic activity and reflectory discharges in sympathetic nerves. Picamilon led to restoration of the initial condition of cerebral hemodynamics disturbed by a previous administration of serotonin.

Randomised double-blind placebo-controlled trial of feverfew in migraine prevention.

Murphy JJ, Heptinstall S, Mitchell JR. Department of Medicine, University Hospital, Nottingham.

Lancet 1988 Jul 23;2(8604):189-92

The use of feverfew (Tanacetum parthenium) for migraine prophylaxis was assessed in a randomised, double-blind, placebo-controlled crossover study. After a one-month single-blind placebo run-in, 72 volunteers were randomly allocated to receive either one capsule of dried feverfew leaves a day or matching placebo for four months and then transferred to the other treatment limb for a further four months. Frequency and severity of attacks were determined from diary cards which were issued every two months; efficacy of each treatment was also assessed by visual analogue scores. 60 patients completed the study and full information was available in 59. Treatment with feverfew was associated with a reduction in the mean number and severity of attacks in each two-month period,

and in the degree of vomiting; duration of individual attacks was unaltered. Visual analogue scores also indicated a significant improvement with feverfew. There were no serious side-effects.

Feverfew (Tanacetum parthenium) as a prophylactic treatment for migraine: A double-blind placebo-controlled study

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Phytotherapy Research (United Kingdom) 1997, 11/7 (508-511)

To assess the effectiveness of feverfew as a prophylactic therapy for migraine, a double-blind placebo controlled cross-over trial was conducted for a period of 4 months. Fifty seven patients who attended an outpatient pain clinic were selected at random and divided into two groups. Both groups were treated with feverfew in the preliminary phase (phase 1), which lasted 2 months, in the second and third phases, which continued for an additional 2 months, a double-blind placebo controlled cross-over study was conducted. The results showed that feverfew caused a significant reduction in pain intensity compared with the placebo treatment. Moreover, a profound reduction was recorded concerning the severity of the typical symptoms that are usually linked to migraine attacks, such as vomiting, nausea, sensitivity to noise and sensitivity to light. Transferring the feverfew -treated group to the placebo treatment resulted in an augmentation of the pain intensity as well as an increase in the severity of the linked symptoms, in contrast, shifting the placebo group to feverfew therapy resulted in a reduction of the pain intensity as well as in the severity of the linked symptoms.

Open label trial of coenzyme Q10 as a migraine preventive.

Rozen TD, Oshinsky ML, Gebeline CA, Bradley KC, Young WB, Shechter AL, Silberstein SD. Jefferson Headache Center/Thomas Jefferson University, Philadelphia, Pennsylvania, USA. RozenT@ccf.org

Cephalalgia. 2002 Mar;22(2):137-41

The objective was to assess the efficacy of coenzyme Q10 as a preventive treatment for migraine headaches. Thirty-two patients (26 women, 6 men) with a history of episodic migraine with or without aura were treated with coenzyme Q10 at a dose of 150 mg per day. Thirty-one of 32 patients completed the study; 61.3% of patients had a greater than 50% reduction in number of days with migraine headache. The average number of days with migraine during the baseline period was 7.34 and this decreased to 2.95 after 3 months of therapy, which was a statistically significant response ($P < 0.0001$). Mean reduction in migraine frequency after 1 month of treatment was 13.1% and this increased to 55.3% by the end of 3 months. Mean migraine attack frequency was 4.85 during the baseline period and this decreased to 2.81 attacks by the end of the study period, which was a statistically significant response ($P < 0.001$). There were no side-effects noted with coenzyme Q10. From this open label investigation

coenzyme Q10 appears to be a good migraine preventive. Placebo-controlled trials are now necessary to determine the true efficacy of coenzyme Q10 in migraine prevention.

Glucosamine for migraine prophylaxis?

Russell AL, McCarty MF. Brampton Pain Clinic, Bramalea, Ontario, Canada.

Med Hypotheses 2000 Sep;55(3):195-8

Following a fortuitous observation that migraine headaches ceased in a patient receiving glucosamine therapy for osteoarthritis, a further ten patients with migraine or migraine-like vascular headaches, refractory to established preventive or abortive therapies, have been treated with daily oral glucosamine. After a lag of 4-6 weeks, a substantial reduction in headache frequency and/or intensity has been noted; in some cases, the benefit appears to be dose-dependent. Since glucosamine can be a rate-limiting precursor for mucopolysaccharide synthesis, it is germane to note previous reports that heparin and pentosan polysulfate may have migraine-preventive activity. There is reason to suspect that mast cells are central mediators of the neurogenic inflammation associated with migraine and cluster headaches. The heparin produced by mast cells may function to provide feedback down-regulation of mast cell activation, and exerts a range of other anti-inflammatory effects. We postulate that supplemental glucosamine can boost mast cell heparin synthesis - perhaps correcting a functional heparin deficiency - thereby preventing or ameliorating the neurogenic inflammation that mediates pain in vascular headache. Whether or not this idea has validity, a controlled study of glucosamine for migraine prophylaxis appears to be warranted.

Prophylactic treatment of migraine with beta-blockers and riboflavin: differential effects on the intensity dependence of auditory evoked cortical potentials.

Sandor PS, Afra J, Ambrosini A, Schoenen J. Neurology Department, CHR Citadelle, University of Liege, Belgium.

Headache 2000 Jan;40(1):30-5

OBJECTIVE: To investigate the influence of different pharmacological treatments on the intensity dependence of auditory evoked cortical potentials in migraineurs.

BACKGROUND: Between attacks, patients with migraine show abnormalities in cortical information processing and decreased brain mitochondrial energy reserve. Both are most probably relevant for migraine pathogenesis, and they could be differentially modified by prophylactic drug therapy. Design.-The intensity dependence of the auditory evoked cortical potentials is, on average, increased in migraine. We have studied this intensity dependence in 26 patients before and after a 4-month period of prophylaxis with beta-blockers (n = 11, all migraine without aura; metoprolol or bisoprolol) or riboflavin (n = 15, migraine without

aura: 13, migraine with aura: 2). Recordings were performed at least 3 days before or after an attack.

RESULTS: After the treatment with beta-blockers, the intensity dependence of the auditory evoked cortical potentials was significantly decreased (before: 1.66+/-1.02 microV/10 dB; after: 0.79+/-1.06 microV/10 dB, P=.02). The decrease in intensity dependence was correlated significantly with clinical improvement (r = .69, P = .02). There was no change in intensity dependence after riboflavin treatment (before: 1.80+/-0.81 microV/10 dB; after: 1.56+/-0.83 microV/10 dB, P = .39), although the majority of patients showed improvement.

CONCLUSIONS: These results confirm that beta-blockers and riboflavin act on two distinct pathophysiological mechanisms. Combining both treatments might enhance their efficacy without increasing central nervous system side effects.

High-dose riboflavin as a prophylactic treatment of migraine: Results of an open pilot study

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Cephalalgia (Norway), 1994, 14/5 (328-329)

If the brain of migraineurs is characterized between attacks by a reduction of mitochondrial phosphorylation potential, riboflavin, which has the potential of increasing mitochondrial energy efficiency, might have prophylactic effects in migraine. In this preliminary open pilot study, 49 patients suffering from migraine (45 without aura, 4 with aura) were treated with 400 mg of riboflavin as a single oral dose for at least 3 months. Twenty-three patients received in addition 75 mg of aspirin. Mean global improvement after therapy was 68.2% and there was no difference between the two groups of patients. With the exception of one patient in the riboflavin plus aspirin group who withdrew because of gastric intolerance, no drug-related side effects were reported. High-dose riboflavin could thus be an effective, low-cost prophylactic treatment of migraine devoid of short-term side effects. A placebo-controlled trial of its efficacy seems worthwhile.

Feverfew and vascular smooth muscle: extracts from fresh and dried plants show opposing pharmacological profiles, dependent upon sesquiterpene lactone content.

Barsby RW; Salan U; Knight DW; Hoult JR Pharmacology Group, King's College London, U.K.

Planta Med (Germany) Feb 1993, 59 (1) p20-5

Preparations of fresh or dried feverfew (Chrysanthemum parthenium) are widely consumed in the U.K. as a remedy for arthritis and migraine, but the pharmacological basis for this has not been established. We have, therefore, compared the properties of extracts of fresh plants with those of dried powdered

leaves available commercially from health food shops. The two extracts differed radically in their content of alpha-methylbutyrolactones and in their pharmacological profile when tested in vitro on the rabbit aortic ring and rat anococcygeus preparations. Extracts of fresh leaves caused does- and time-dependent inhibition of the contractile responses of aortic rings to all receptor-acting agonists so far tested; the effects were irreversible and may represent a toxic modification of post-receptor contractile function in the smooth muscle. The presence of potentially -SH reactive parthenolide and other sesquiterpene alphamethylenebutyrolactones in these extracts, and the close parallelism of the actions of pure parthenolide, suggest that the inhibitory effects are due to these compounds. In contrast, chloroform extracts of dried powdered leaves were not inhibitory but themselves elicited potent and sustained contractions of aortic smooth muscle that were not antagonised by ketanserin (5-HT2 receptor antagonist). These extracts did not contain parthenolide or butyrolactones according to a chemical-HPLC assay, We conclude that there are marked differences in the pharmacological potency and profiles between preparations from fresh and dried feverfew and that this may relate to their lactone content. As the effects of the lactones are potentially toxic, it will be necessary to compare the clinical profiles and side effects of preparations obtained from the two sources.

Inhibition of 5-lipoxygenase and cyclo-oxygenase in leukocytes by feverfew. Involvement of sesquiterpene lactones and other components.

Sumner H; Salan U; Knight DW; Hoult JR Pharmacology Group, King's College London, U.K.

Biochem Pharmacol (England) Jun 9 1992, 43 (11) p2313-20

Leaves or infusions of feverfew, Tanacetum parthenium, have long been used as a folk remedy for fever, arthritis and migraine, and derived products are widely available in U.K. health food shops. Previous reports have suggested interactions with arachidonate metabolism. Crude chloroform extracts of fresh feverfew leaves (rich in sesquiterpene lactones) and of commercially available powdered leaves (lactone-free) produced dose-dependent inhibition of the generation of thromboxane B2 (TXB2) and leukotriene B4 (LTB4) by ionophore- and chemoattractant-stimulated rat peritoneal leukocytes and human polymorphonuclear leukocytes. Approximate IC50 values were in the range 5-50 micrograms/mL, and inhibition of TXB2 and LTB4 occurred in parallel. Isolated lactones (parthenolide, epoxyartemorin) treated with cysteine (to neutralize reactive alpha-methylene butyrolactone functions of the sesquiterpenes). Inhibition of eicosanoid generation appeared to be irreversible but not time-dependent. We conclude that feverfew contains a complex mixture of sesquiterpene lactone and non-sesquiterpene lactone inhibitors of eicosanoid synthesis of high potency, and that these biochemical actions may be relevant to the claimed therapeutic actions of the herb.

Efficacy of feverfew as prophylactic treatment of migraine.

Johnson ES; Kadam NP; Hylands DM; Hylands PJ

Br Med J (Clin Res Ed) (England) Aug 31 1985, 291 (6495) p569-73

Seventeen patients who ate fresh leaves of feverfew daily as prophylaxis against migraine participated in a double blind placebo controlled trial of the herb: eight patients received capsules containing freeze dried feverfew powder and nine placebo. Those who received placebo had a significant increase in the frequency and severity of headache, nausea, and vomiting with the emergence of untoward effects during the early months of treatment. The group given capsules of feverfew showed no change in the frequency or severity of symptoms of migraine. This provides evidence that feverfew taken prophylactically prevents attacks of migraine, and confirmatory studies are now indicated, preferably with a formulation controlled for sesquiterpene lactone content, in migraine sufferers who have never treated themselves with this herb.

Herbal therapy for migraine: An unconventional approach

Diamond S. Inpatient Headache Unit at Louis A. Weiss Memorial Hospital, Chicago, IL United States

Postgraduate Medicine (United States) 1987, 82/1 (197-198)

A pilot study was conducted at the City of London Migraine Clinic to establish whether feverfew 's efficacy could be shown through orthodox clinical evaluation and also to demonstrate any adverse effects on cellular and chemical elements of the blood. Because of possible ethical objections, only patients who had previously consumed feverfew leaves were included in the study.

Platelet ionized magnesium, cyclic AMP, and cyclic GMP levels in migraine and tension-type headache.

Mishima K; Takeshima T; Shimomura T; Okada H; Kitano A; Takahashi K; Nakashima K Division of Neurology, Tottori University Faculty of Medicine, Yonago, Japan.

Headache (United States) Oct 1997, 37 (9) p561-4

Decreased serum and intracellular levels of magnesium have been reported in patients with migraine . It has been suggested that magnesium may play an important role in the attacks and pathogenesis of headaches. We measured ionized magnesium, cyclic AMP (adenosine monophosphate), and cyclic GMP (guanosine monophosphate) in platelets of patients with migraine, in patients with tension-type headache, and in healthy controls. The platelet level of ionized magnesium from patients with tension-type headache was significantly lower than the levels from the other two groups. The platelet level of cyclic AMP from patients with migraine was higher than those from the other groups. We found no significant differences in the platelet cyclic GMP levels among the three groups. It is suggested that reduced platelet ionized magnesium in patients with tension-type headache is related to abnormal platelet function, and that increased platelet

cyclic AMP in patients with migraine is related to alteration of neurotransmitters in the platelet.

Omega- 3: Essential for good health

Pelton R.

American Druggist (United States) 1997, 214/7 (52-53)

Supplements of omega -3 fatty acids may be needed to maintain a careful balance with omega-6 and regulate the production of prostaglandins and their effects.

Magnesium taurate and fish oil for prevention of migraine.

McCarty MF Nutrition 21, San Diego, CA 92109, USA.

Med Hypotheses (England) Dec 1996, 47 (6) p461-6

Although the pathogenesis of migraine is still poorly understood, various clinical investigations, as well as consideration of the characteristic activities of the wide range of drugs known to reduce migraine incidence, suggest that such phenomena as neuronal hyperexcitation, cortical spreading depression, vasospasm, platelet activation and sympathetic hyperactivity often play a part in this syndrome. Increased tissue levels of taurine, as well as increased extracellular magnesium, could be expected to dampen neuronal hyperexcitation, counteract vasospasm, increase tolerance to focal hypoxia and stabilize platelets; taurine may also lessen sympathetic outflow. Thus it is reasonable to speculate that supplemental magnesium taurate will have preventive value in the treatment of migraine. Fish oil, owing to its platelet-stabilizing and antivasospastic actions, may also be useful in this regard, as suggested by a few clinical reports. Although many drugs have value for migraine prophylaxis, the two nutritional measures suggested here may have particular merit owing to the versatility of their actions, their safety and lack of side-effects and their long-term favorable impact on vascular health. (94 Refs.)

Prophylaxis of migraine with oral magnesium: results from a prospective, multi-center, placebo-controlled and double-blind randomized study.

Peikert A; Wilimzig C; Kohne-Volland R Department of Neurology and Clinical Neurophysiology, Munich-Harlaching Clinic, Germany.

Cephalalgia (Norway) Jun 1996, 16 (4) p257-63

In order to evaluate the prophylactic effect of oral magnesium, 81 patients aged 18-65 years with migraine according to the International Headache Society (IHS) criteria (mean attack frequency 3.6 per month) were examined. After a prospective baseline period of 4 weeks they received oral 600 mg (24 mmol) magnesium (trimagnesium dicitrate) daily for 12 weeks or placebo. In weeks 9-12 the attack frequency was reduced by 41.6% in the magnesium group and by

15.8% in the placebo group compared to the baseline ($p < 0.05$). The number of days with migraine and the drug consumption for symptomatic treatment per patient also decreased significantly in the magnesium group. Duration and intensity of the attacks and the drug consumption per attack also tended to decrease compared to placebo but failed to be significant. Adverse events were diarrhea (18.6%) and gastric irritation (4.7%). High-dose oral magnesium appears to be effective in migraine prophylaxis.

Electromyographical ischemic test and intracellular and extracellular magnesium concentration in migraine and tension-type headache patients.

Mazzotta G; Sarchielli P; Alberti A; Gallai V Interuniversity (Perugia-Rome-Sassari-Bari) Centre for the Study of Headache and Neurotransmitter Disorders of the CNS, Italy.

Headache (United States) Jun 1996, 36 (6) p357-61

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Nocturnal melatonin excretion is decreased in patients with migraine without aura attacks associated with menses

Brun J.; Claustrat B.; Saddier P.; Chazot G.

Cephalalgia (Norway), 1995, 15/2 (136-139)

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Urinary melatonin excretion throughout the ovarian cycle in menstrually related migraine

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Cephalalgia 1994 Jun;14(3):205-9

Nocturnal urinary melatonin excretion was significantly decreased throughout an ovarian cycle in 12 migraine without aura patients compared to 8 healthy controls. Normal increases in urinary melatonin excretion during the luteal phase was less pronounced in the migraine patients. Melatonin excretion was further decreased during headache. The data indicate impaired pineal function in migraine.

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The influence of the pineal gland on migraine and cluster headaches and effects of treatment with picoTesla magnetic fields.

Sandyk R

Int J Neurosci (England) Nov-Dec 1992, 67 (1-4) p145-71

For over half a century the generally accepted views on the pathogenesis of migraine were based on the theories of Harold Wolff implicating changes in cerebral vascular tone in the development of migraine. Recent studies, which are based on Leao's concept of spreading depression, favor primary neuronal injury with secondary involvement of the cerebral circulation. In contrast to migraine, the pathogenesis of cluster headache (CH) remains entirely elusive. Both migraine and CH are cyclical disorders which are characterised by spontaneous exacerbations and remissions, seasonal variability of symptoms, and a relationship to a variety of environmental trigger factors. CH in particular has a strong circadian and seasonal regularity. It is now well established that the pineal gland is an adaptive organ which maintains and regulates cerebral homeostasis by "fine tuning" biological rhythms through the mediation of melatonin. Since migraine and CH reflect abnormal adaptive responses to environmental influences resulting in heightened neurovascular reactivity, I propose that the pineal gland is a critical mediator in their pathogenesis. This novel hypothesis provides a framework for future research and development of new therapeutic modalities for these chronic headache syndromes. The successful treatment of a patient with an acute migraine attack with external magnetic fields, which acutely inhibit melatonin secretion in animals and humans, attests to the importance of the pineal gland in the pathogenesis of migraine headache. (242 Refs.)

Is migraine due to a deficiency of pineal melatonin?

Toglia JU

Ital J Neurol Sci (Italy) Jun 1986, 7 (3) p319-23

Recent clinical observations favor the theory that migraine is caused by a primary injury of cerebral neurons with secondary involvement of intracranial and extracranial blood vessels. The primary injury is attributed to disruption of cerebral neurotransmitters and particularly the neuroadrenergic and serotonergic systems. These theories have not explained the importance of environmental factors, which so frequently trigger migraine. The author suggests that the pineal gland, which is outside the CNS unprotected by blood brain barrier and sensitive to external stimuli, could act as the intermediate causative factor of migraine, via a derangement of melatonin. (47 Refs.)

FEVERFEW (Tanacetum pathenium):

Feverfew appears to work in the treatment and prevention of migraine headaches by inhibiting the release of blood vessel dilating substances from platelets (serotonin and histamine), inhibiting the production of inflammatory substances (leukotrienes, serine proteases, etc.), and re-establishing proper blood vessel tone. Commercial sources providing assurance of botanical identity and minimum

required level of parthenolides are needed (Awang DVC. Feverfew. Car Pharm J 122:266-70, 1989).

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Note: The efficacy of feverfew is dependent upon adequate levels of parthenolide, the active ingredient. (The preparations used in successful clinical trials have a parthenolide content of 0.4-0.66%.)

Animal Ex vivo Study: Extracts of fresh feverfew caused a dose- and time dependent, irreversible inhibition of the contractile response of rabbit aortic rings to all receptor-acting agonists tested. The presence of potentially SH reacting parthenolide and other sesquiterpene alpha-methylenebutyrolactones in, these extracts, and the close parallelism of pure parthenolide, suggest that the inhibitory effects are due to these compounds. Extracts of the dry leaves were not inhibitory and actually caused potent and sustained contractions of aortic smooth muscle; these extracts were found to be devoid or parthenolide or butyrolactones (Barsby RWJ, Salan U, Knight BW, Hoult JRS. Feverfew and vascular smooth muscle: Extracts from fresh and dried plants show opposing pharmacological profiles, dependent upon sesquiterpene lactone content. Planta Medica 59:20-5, 1993).

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Nocturnal plasma melatonin profile and melatonin kinetics during infusion in status migrainosus

Claustrat B.; Brun J.; Geoffriau M.; Zaidan R.; Mallo C.; Chazot G.
B. Claustrat, Serv. Radiopharmacie/Radioanalyse, Hopital Neurologique, 59 Boulevard Pinel, 69003 Lyon France
Cephalalgia (Norway), 1997, 17/4 (511-517)

The plasma melatonin profile was significantly disturbed (phase-shift of the maximum melatonin level) in four out of six female sufferers from status migrainosus, compared with nine healthy controls. The number of secretion peaks was similar in both groups. A nocturnal 20 pg melatonin infusion (from 21.00 to 01.00 h) evoked plasma melatonin levels slightly higher than a physiological secretion peak. During infusion, the episodes of secretion were reinforced and the endogenous plasma profile was phase-advanced in two patients displaying a phase-delay. These data suggest impaired pineal function in migraine. In the absence of side effects of melatonin infusion, the relief of certain migraine symptoms described by our patients might support a controlled trial of melatonin in migraine.

Magnesium taurate and fish oil for prevention of migraine.

McCarty MF
Nutrition 21, San Diego, CA 92109, USA.
Med Hypotheses (England) Dec 1996, 47 (6) p461-6

Although the pathogenesis of migraine is still poorly understood, various clinical investigations, as well as consideration of the characteristic activities of the wide range of drugs known to reduce migraine incidence, suggest that such phenomena as neuronal hyperexcitation, cortical spreading depression, vasospasm, platelet activation and sympathetic hyperactivity often play a part in this syndrome. Increased tissue levels of taurine, as well as increased extracellular magnesium, could be expected to dampen neuronal hyperexcitation, counteract vasospasm, increase tolerance to focal hypoxia and stabilize platelets; taurine may also lessen sympathetic outflow. Thus it is reasonable to speculate that supplemental magnesium taurate will have preventive value in the treatment of migraine. Fish oil, owing to its platelet-stabilizing and antivasospastic actions, may also be useful in this regard, as suggested by a few clinical reports. Although many drugs have value for migraine prophylaxis, the two nutritional measures suggested here may have particular merit owing to the versatility of their actions, their safety and lack of side-effects and their long-term favorable impact on vascular health. (94 Refs.)

Prophylaxis of migraine with oral magnesium: results from a prospective, multi-center, placebo-controlled and double-blind randomized study.

Peikert A; Wilimzig C; Kohne-Volland R
Department of Neurology and Clinical Neurophysiology, Munich-Harlaching Clinic, Germany.
Cephalalgia (Norway) Jun 1996, 16 (4) p257-63

In order to evaluate the prophylactic effect of oral magnesium, 81 patients aged 18-65 years with migraine according to the International Headache Society (IHS) criteria (mean attack frequency 3.6 per month) were examined. After a prospective baseline period of 4 weeks they received oral 600 mg (24 mmol) magnesium (trimagnesium dicitrate) daily for 12 weeks or placebo. In weeks 9-12 the attack frequency was reduced by 41.6% in the magnesium group and by 15.8% in the placebo group compared to the baseline ($p < 0.05$). The number of days with migraine and the drug consumption for symptomatic treatment per patient also decreased significantly in the magnesium group. Duration and intensity of the attacks and the drug consumption per attack also tended to decrease compared to placebo but failed to be significant. Adverse events were diarrhea (18.6%) and gastric irritation (4.7%). High-dose oral magnesium appears to be effective in migraine prophylaxis.

Electromyographical ischemic test and intracellular and extracellular magnesium concentration in migraine and tension-type headache patients.

Mazzotta G; Sarchielli P; Alberti A; Gallai V
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basis of migraine and tension-type headache. Migraine seems to be related to an altered magnesium status, which manifests itself by a neuromuscular hyperexcitability and a reduced concentration in red blood cells.

Herbal products begin to attract the attention of brand-name drug companies.

Cottrell K
Can Med Assoc J (Canada) Jul 15 1996, 155 (2) p216-9

Many Canadians are interested in alternative medicine, and burgeoning public interest in herbal remedies has not gone unnoticed by Canada's drug companies. McNeil Consumer Products recently began selling a migraine prophylaxis made from the plant feverfew. Physicians who would like to see herbal medications subjected to outcome studies and quality-control standards, with evidence of risks and benefits being made available to consumers, welcome the interest the companies are showing. Meanwhile, physicians and pharmacists are trying to respond to consumer demand by increasing their own knowledge about herbal medications.

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Melatonin in humans physiological and clinical studies.

Wetterberg L
J Neural Transm Suppl (Austria) 1978, (13) p289-310

Studies are reported of the variation of melatonin in serum, plasma urine and cerebrospinal fluid in normal subjects and in patients with various diseases. The diurnal variation of plasma and urine melatonin found in healthy controls on a regular dark-sleep pattern persisted when the subjects slept in light. The effect of sleep deprivation and of rapid light exposure at night is reported. There was a correlation between melatonin in morning urine and plasma at 2 a.m. Four hours of extended darkness in the morning as well as a 9-hour shift of sleep and activity cycles following travel affected the melatonin rhythm. The night increase in plasma melatonin preceeded both the cortisol and prolactin rise. A single oral dose of 4.3 X 10(5) nmol of melatonin given to a 44-year-old healthy male gave a peak plasma value of 624 nmol/l after 30 min. Plasma melatonin was not affected by electroconvulsive therapy, TRH-injection, L-Dopa or bromoergocryptine orally. Patients with alcoholism, migraine, postoperative pinealoma, panhypopituitarism, hereditary dystonia and schizophrenics on propranolol exhibited a decreased amplitude of their diurnal rhythm of melatonin. Two patients with pituitary tumors had occasional high levels of plasma melatonin. The change in melatonin secretion in human is apparently controlled by a mechanism which is at least party influenced by environmental lighting conditions, drugs and different disease states. (27 refs.)

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21. Multiple Sclerosis

Multi nutrient, fish oil, acetyl-L- carnitine, alpha-lipoic acid, coenzyme Q10, vitamin B12, soy lecithin.

Folate, vitamin B12, and neuropsychiatric disorders.

Bottiglieri T Kimberly H. Courtwright and Joseph W. Summers Institute of Metabolic Disease, Baylor University Medical Center, Dallas, Texas, USA.

Nutr Rev (United States) Dec 1996, 54 (12) p382-90

Folate and vitamin B12 are required both in the methylation of homocysteine to methionine and in the synthesis of S-adenosylmethionine. S-adenosylmethionine is involved in numerous methylation reactions involving proteins, phospholipids, DNA, and neurotransmitter metabolism. Both folate and vitamin B12 deficiency may cause similar neurologic and psychiatric disturbances including depression, dementia, and a demyelinating myelopathy. A current theory proposes that a defect in methylation processes is central to the biochemical basis of the neuropsychiatry of these vitamin deficiencies. Folate deficiency may specifically affect central monoamine metabolism and aggravate depressive disorders. In addition, the neurotoxic effects of homocysteine may also play a role in the neurologic and psychiatric disturbances that are associated with folate and vitamin B12 deficiency.

1,25-dihydroxyvitamin D3 reversibly blocks the progression of relapsing encephalomyelitis, a model of multiple sclerosis

Cantorna M.T.; Hayes C.E.; DeLuca H.F. Department of Biochemistry, 420 Henry Mall, University of Wisconsin, Madison, WI 53706 USA

Proceedings of the National Academy of Sciences of the United States of America (USA), 1996, 93/15 (7861-7864)

Experimental autoimmune encephalomyelitis (EAE) is an autoimmune disease believed to be a model for the human disease multiple sclerosis (MS). Induced by immunizing B10.PL mice with myelin basic protein (MBP). EAE was completely prevented by the administration of 1,25-dihydroxy vitamin D3 (1,25- (OH)2D3). 1,25-(OH)2D3 could also prevent the progression of EAE when administered at the appearance of the first disability symptoms. Withdrawal of 1,25-(OH)2D3 resulted in a resumption of the progression of EAE. Thus, the block by 1,25-(OH)2D3 is reversible. A deficiency of vitamin D resulted in an increased susceptibility to EAE. Thus, 1,25-(OH)2D3 or its analogs are potentially important for treatment of MS

Exogenous lipids in myelination and myelination.

Di Biase A; Salvati S Dept. of Metabolism and Pathological Biochemistry, Istituto Superiore di Sanita, Rome, Italy.

Kao Hsiung I Hsueh Ko Hsueh Tsa Chih (Taiwan) Jan 1997 , 13 (1) p19-29

Myelinogenesis is a scheduled process that depends on both the intrinsic properties of the cell and extracellular signals. In rat brain, myelin development is an essentially postnatal event and environmental interferences could affect myelin synthesis. Nutrition plays an important role, since severe postnatal malnutrition and essential fatty acid (EFA) deficiency cause hypomyelination. Even though the dietary effects are more pronounced in the postnatal period, dietary lipids can affects myelin development also in the postweaning period. Rats fed with diets rich in polyunsaturated n3 fatty acids showed a decrease of the relative amount of myelin basic protein (MBP) and a CNPase activity indicating a delay in myelin deposition and/or an instability of its structure. Our recent studies have shown that dietary fatty acids can be positively involved in the control of central nervous system (CNS) myelinogenesis. Offspring of rats fed diets containing odd chain fatty acid during pregnancy and lactation show an early development of behavioral reflexes linked to myelination compared to controls fed a diet containing margarine. Subsequent studies have shown that the expression of myelin proteins is higher in test than in control animals, but the mechanism of the action of fatty acids is still unknown. Also human brain myelinogenesis can be affected by environmental factors. EFA deficiency has been well studied for the important role of C22:6 (a C18:3 metabolite) in the vision system development. The observation that dietary fatty acids can affect membrane composition has led to the use of modified diets in some CNS pathological conditions. For example, preterm infants characterized by low levels of C22:6 and fed with formulae diets enriched in this fatty acid, show a recovery of visual function. The administration of C22:6 has also been tested in patients affected by peroxisomal biogenesis disorders which are associated with very low levels of this fatty acid in the brain. During the treatment, C22:6 content increases in red blood cells, and probably in the brain membranes, as considerable neurologic and electrophysiological improvement suggest. A mixture of glyceryltrierucate and glyceryltrioleate has been tested in the demyelinating disease Adrenoleukodistrophy which is characterized by an abnormal accumulation of very long chain fatty acids (VLCFA) in tissues and fluids. The diet is able to lower VLCFA levels in plasma, but its efficacy for myelin damage is debated. Lastly, a diet which reduces the intake of saturated fatty acid and increases the quantity of polyunsaturates is suggested for multiple sclerosis patients since a decrease of linoleic acid in their plasma and erythrocytes has been observed. Such a diet seems able to reduce the severity of the attacks. (85 Refs.)

Nutritional factors in the aetiology of multiple sclerosis: A case-control study in Montreal, Canada

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International Journal of Epidemiology (UnitedKingdom) 1998, 27/5 (845-852)

Background. It has been suggested that nutrition and food patterns, particularly high consumption of animal fat and low intake of fish products, may play a role in the aetiology of multiple sclerosis (MS).

Methods. The relation between nutritional factors and MS was studied among 197 incident cases and 202 frequency matched controls in metropolitan Montreal during 1992-1995. Dietary information was collected by employing a 164-item food frequency questionnaire in a face-to-face interview.

Results. An inverse association was observed between high body mass index (BMI) and the risk of MS, with an odds ratio (OR) of 0.76 (95% confidence interval [CI] 0.61-0.95), per 5-unit increase in BMI, both sexes combined. In addition, taller women showed a greater risk for MS; the OR per 10 cm increase in height was 1.58 (95% CI: 1.06-2.35). In continuous variable analyses, using the difference between the lowest and highest quartile of intake as a unit, a positive association was observed with energy and animal fat intake. The OR per 897 kcal increase was 2.03 (95% CI: 1.13-3.67) and 1.99 (95% CI: 1.12-3.54) per 33 g of animal fat intake above the baseline. A significant protective effect was observed with other nutrients, including vegetable protein, dietary fibre, cereal fibre, vitamin C, thiamin, riboflavin, calcium, and potassium. Similar trends were seen for males and females when analysed separately. With respect to specific foods (as opposed to nutrients), a higher intake of fruit juices was inversely associated with risk (OR = 0.82; 95% CI: 0.74-0.92). A protective effect was also observed with cereal/breads intake for all cases combined (OR = 0.62; 95% CI: 0.40-0.97) and for fish among women only; pork/hot dogs (OR = 1.24; 95% CI: 1.02-1.51) and sweets/candy (OR = 1.29; 95% CI: 1.07-1.55) were positively associated with risk.

Conclusion. The study generally supports a protective role for components commonly found in plants (fruit/vegetables and grains) and an increased risk with high energy and animal food intake.

Multiple sclerosis: Decreased relapse rate through dietary supplementation with calcium, magnesium and vitamin D

Goldberg P, Fleming MC, Picard EH

Med. Hypotheses (UK), 1986, 21/2 (193-200)

A group of young patients having multiple sclerosis was treated with dietary supplements containing calcium, magnesium and vitamin D for a period of one to two years. The experimental design employed self-pairing: the response of each patient was compared with his/her own case history as control. The number of

exacerbations observed during the program was less than one half the number expected from case histories. No side effects were apparent. The dietary regimen may offer a new means of controlling the exacerbation rate in MS, at least for younger patients. The results tend to support a theory of MS which states that calcium and magnesium are important in the development, structure and stability of myelin.

Vitamin D and multiple sclerosis.

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Proc Soc Exp Biol Med (United States) Oct 1997, 216 (1) p21-7

Recently, it has been clearly demonstrated that exogenous 1,25-dihydroxyvitamin D3, the hormonal form of vitamin D3 , can completely prevent experimental autoimmune encephalomyelitis (EAE), a widely accepted mouse model of human multiple sclerosis (MS). This finding has focused attention on the possible relationship of this disease to vitamin D. Although genetic traits certainly contribute to MS susceptibility, an environmental factor is also clearly involved. It is our hypothesis that one crucial environmental factor is the degree of sunlight exposure catalyzing the production of vitamin D3 in skin, and, further, that the hormonal form of vitamin D3 is a selective immune system regulator inhibiting this autoimmune disease. Thus, under low-sunlight conditions, insufficient vitamin D3 is produced, limiting production of 1,25-dihydroxyvitamin D3, providing a risk for MS. Although the evidence that vitamin D3 is a protective environmental factor against MS is circumstantial, it is compelling. This theory can explain the striking geographic distribution of MS, which is nearly zero in equatorial regions and increases dramatically with latitude in both hemispheres. It can also explain two peculiar geographic anomalies, one in Switzerland with high MS rates at low altitudes and low MS rates at high altitudes, and one in Norway with a high MS prevalence inland and a lower MS prevalence along the coast. Ultraviolet (UV) light intensity is higher at high altitudes, resulting in a greater vitamin D3 synthetic rate, thereby accounting for low MS rates at higher altitudes. On the Norwegian coast, fish is consumed at high rates and fish oils are rich in vitamin D3 . Further, experimental work on EAE provides strong support for the importance of vitamin D3 in reducing the risk and susceptibility for MS. If this hypothesis is correct, then 1,25-dihydroxyvitamin D3 or its analogs may have great therapeutic potential in patients with MS. More importantly, current research together with data from migration studies opens the possibility that MS may be preventable in genetically susceptible individuals with early intervention strategies that provide adequate levels of hormonally active 1,25-dihydroxyvitamin D3 or its analogs. (65 Refs.)

The possible role of gradual accumulation of copper, cadmium, lead and iron and gradual depletion of zinc, magnesium, selenium, vitamins B2, B6, D, and E and essential fatty acids in multiple sclerosis.

Johnson S.

Med Hypotheses 2000 Sep;55(3):239-41

Multiple sclerosis (MS) has a much higher incidence among caucasians that in any other race. Furthermore: females are much more susceptible than males and white females living in colder, wetter areas are much more susceptible than those living in warmer areas. On the other hand, menstruating women have increased copper (Cu) absorption and half-life, so they tend to accumulate more Cu than males. Moreover, rapidly growing girls have an increased demand for zinc (Zn), but their rapidly decreasing production of melatonin results in impaired Zn absorption, which is exacerbated by the high Cu levels. The low Zn levels result in deficient CuZnSuperoxide dismutase (CuZnSOD), which in turn leads to increased levels of superoxide. Menstruating females also often present with low magnesium (Mg) and vitamin B6 levels. Vitamin B6 moderates intracellular nitric oxide (NO) production and extracellular Mg is required for NO release from the cell, so that a deficiency of these nutrients results in increased NO production in the cell and reduced release from the cell. The trapped NO combines with superoxide to form peroxinitrite, an extremely powerful free radical that leads to the myelin damage of MS. Iron (Fe), molybdenum (Mo) and cadmium (Cd) accumulation also increase superoxide production. Which explains MS in males, who tend to accumulate Fe much faster and Cu much less rapidly than females. Since vitamin D is paramount for Mg absorption, the much reduced exposure to sunlight in the higher latitudes may account for the higher incidence in these areas. Moreover, vitamin B2 is a cofactor for xanthine oxidase, and its deficiency exacerbates the low levels of uric acid caused by high Cu levels, resulting in myelin degeneration. Finally Selenium (Se) and vitamin E prevent lipid peroxidation and EPA and DHA upregulate CuZnSOD. Therefore, supplementation with 100 mg MG, 25 mg vit B6, 10 mg vit B2, 15 mg Zn and 400 IU vit D and E, 100 < mgr;g Se, 180 mg EPA and 120 mg DHA per day between 14 and 16 years of age may prevent MS.

Vitamin B12 metabolism and massive-dose methyl vitamin B12 therapy in Japanese patients with multiple sclerosis.

Kira J; Tobimatsu S; Goto I Department of Neurology, Faculty of Medicine, Kyushu University, Fukuoka.

Intern Med (Japan) Feb 1994, 33 (2) p82-6

Serum vitamin B12 levels and unsaturated vitamin B12 binding capacities were measured in 24 patients with multiple sclerosis (MS), 73 patients with other neurological disorders and 21 healthy subjects. There was no decrease in the vitamin B12 levels, however, a significant decrease in the unsaturated vitamin B12 binding capacities was observed in patients with MS when compared with other groups. A massive dose of methyl vitamin B12 (60 mg every day for 6 months) was administered to 6 patients with chronic progressive MS, a disease which usually had a morbid prognosis and widespread demyelination in the central nervous system. Although the motor disability did not improve clinically, the abnormalities in both the visual and brainstem auditory evoked potentials improved more frequently during the therapy than in the pre-treatment period. We

therefore consider that a massive dose methyl vitamin B12 therapy may be useful as an adjunct to immunosuppressive treatment for chronic progressive MS.

CLINICAL CORRESPONDENCE: the effect of magnesium oral therapy on spasticity in a patient with multiple sclerosis.

Rossier P, van Erven S, Wade DT. Rivermead Rehabilitation Centre, Abingdon Road, Oxford OX1 4XD, UK.

Eur J Neurol 2000 Nov;7(6):741-4

The effects of magnesium glycerophosphate oral therapy on spasticity was studied in a 35-year-old woman with severe spastic paraplegia resulting from multiple sclerosis (MS). We found a significant improvement in the spasticity after only 1 week from the onset of the treatment on the modified Ashworth scale, an improvement in the range of motion and in the measures of angles at resting position in lower limbs. No side-effects were reported and there was no weakness in the arms during the treatment.

Vitamin B12 and its relationship to age of onset of Kira J. et al. 1994 multiple sclerosis.

Sandyk R; Awerbuch GI NeuroCommunication Research Laboratories, Danbury, CT 06811.

Int J Neurosci (England) Jul-Aug 1993, 71 (1-4) p93-9

Attention has been focused recently on the association between vitamin B12 metabolism and the pathogenesis of multiple sclerosis (MS). Several recent reports have documented vitamin B12 deficiency in patients with MS. The etiology of this deficiency in MS is unknown. The majority of these patients do not have pernicious anemia and serum levels of the vitamin Are unrelated to the course or chronicity of the disease. Moreover, vitamin B12 does not reverse the associated macrocytic anemia nor are the neurological deficits of MS improved following supplementation with vitamin B12 . It has been suggested that vitamin B12 deficiency may render the patient more vulnerable to the putative viral and/or immunologic mechanisms widely suspected in MS. In the present communication, we report that serum vitamin B12 levels in MS patients are related to the age of onset of the disease. Specifically, we found in 45 MS patients that vitamin B12 levels were significantly lower in those who experienced the onset of first neurological symptoms prior to age 18 years (N = 10) compared to patients in whom the disease first manifested after age 18 (N = 35). In contrast, serum folate levels were unrelated to age of onset of the disease. As vitamin B12 levels were statistically unrelated to chronicity of illness, these findings suggest a specific association between the timing of onset of first neurological symptoms of MS and vitamin B12 metabolism. In addition, since vitamin B12 is required for the formation of myelin and for immune mechanisms, we propose that its deficiency in MS is of critical pathogenetic significance.

Experimental and clinical studies on dysregulation of magnesium metabolism and the aetiopathogenesis of multiple sclerosis.

Yasui M, Ota K. Division of Neurological Diseases, Wakayama Medical College, Japan.

Magnes Res 1992 Dec;5(4):295-302

The proposed aetiologies of multiple sclerosis (MS) have included immunological mechanisms, genetic factors, virus infection and direct or indirect action of minerals and/or metals. The processes of these aetiologies have implicated magnesium. Magnesium and zinc have been shown to be decreased in central nervous system (CNS) tissues of MS patients, especially tissues such as white matter where pathological changes have been observed. The calcium content of white matter has also been found to be decreased in MS patients. The interactions of minerals and/or metals such as calcium, magnesium, aluminium and zinc have also been evaluated in CNS tissues of experimental animal models. These data suggest that these elements are regulated by pooling of minerals and/or metals in bones. Biological actions of magnesium may affect the maintenance and function of nerve cells as well as the proliferation and synthesis of lymphocytes. A magnesium deficit may induce dysfunction of nerve cells or lymphocytes directly and/or indirectly, and thus magnesium depletion may be implicated in the aetiology of MS. The action of zinc helps to prevent virus infection, and zinc deficiency in CNS tissues of MS patients may also be relevant to its aetiology. Magnesium interacts with other minerals and/or metals such as calcium, zinc and aluminium in biological systems, affecting the immune system and influencing the content of these elements in CNS tissues. Because of these interactions, a magnesium deficit could also be a risk factor in the aetiology of MS.

Homocysteine and vitamin B12 in multiple sclerosis

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Biogenic Amines (Netherlands) 1995, 11/6 (479-485)

The levels of cobalamin and homocysteine in patients with multiple sclerosis (MS) were evaluated. The mean value of cobalamin (B12) in serum and cerebrosphinal fluid (CSF) in MS patients were 0.176 +/- 0.0177 and 0.059 +/- 0.003 mumol/l respectively whereas the levels were 0.317 +/- 0.02 and 0.081 +/- 0.005 mumol/l respectively in the healthy subjects. The mean homocysteine (HC) levels in serum and CSF in MS patients were 13.05 +/- 0.54 and 3.07 +/- 0.15 mumol/l respectively as compared to 2.85 +/- 0.15 and 1.06 +/- 0.07 in the healthy subjects. The increased levels of HC and decreased levels in B12 in serum as well as in CSF in MS patients were significant ($p < 0.001$) as compared to healthy subjects. Our finding indicate that MS patients are particularly prone to B12 deficiency resulting into increased levels of HC both in serum and CSF and this even subtle biochemical signs of abnormality seems to justify B6 and B12 treatment.

Measurement of low-molecular-weight antioxidants, uric acid, tyrosine and tryptophan in plaques and white matter from patients with multiple sclerosis.

Langemann H, Kabiersch A, Newcombe J Department of Research, Cantonal Hospital Basel, Switzerland.

Eur Neurol (Switzerland) 1992, 32 (5) p248-52

The levels of the antioxidants ascorbic acid, cysteine, reduced glutathione and alpha-tocopherol, of the free-radical marker uric acid and of the amino acids tyrosine and tryptophan were measured by means of high-pressure liquid chromatography in plaques, adjacent white matter and distant white matter from patients with multiple sclerosis, and in central nervous system tissue from patients without neurological diseases. Cholesterol and DNA were also determined, to check demyelination and cellularity. Uric acid was increased and glutathione correspondingly decreased in plaques; alpha-tocopherol was lowest in plaques and highest in distant white matter in all cases. Ascorbic acid, cysteine, tyrosine and tryptophan were not significantly changed in any tissue. The results provide evidence supporting the involvement of free radicals in multiple sclerosis.

Clinical trials of unsaturated fatty acids in multiple sclerosis

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IRCS Med. Sci. (England), 1981, 9/12 (1081)

The membrane of MS-RBC (multiple sclerosis-erythrocytes) is different from non-MS. Until now it was believed that 6-8 months treatment with gamma-linolenate converted their abnormal properties into normal, as judged by electrophoretic measurements in the presence of LA (linoleic acid) and AA (arachidonic acid). Further experimentation has shown however, such conversion to non-MS type is delayed until 21-24 months after gamma-linolenate feeding, when low doses of LA and AA begin to have the same effect on mobility as they do in normal cells. Thus any clinical trial of PUFA should begin about 2 years after it is instituted - not concluded, as at present. This may account for the relative success of Swank's dietary treatment which spans over 20 years. The long term requirement for essential fatty acids (EFA) to restore membrane normality in MS must be taken into account in planning therapeutic trials.

Dietary polyunsaturated fatty acids and depression: When cholesterol does not satisfy

Hibbeln JR, Salem N Jr Laboratory of Membrane Biophysics and Biochemistry, DICBR, National Institute of Alcohol Abuse and Alcoholism, Rockville, MD 20852, USA.

American Journal of Clinical Nutrition (USA), 1995, 62/1 (1-9)

Recent studies have both offered and contested the proposition that lowering plasma cholesterol by diet and medications increases suicide, homicide, and depression. Significant confounding factors include the quantity and distribution of dietary n-6 and n-3 polyunsaturated essential fatty acids that influence serum lipids and alter the biophysical and biochemical properties of cell membranes. Epidemiological studies in various countries and in the United States in the last century suggest that decreased n-3 fatty acid consumption correlates with increasing rates of depression. This is consistent with a well-established positive correlation between depression and coronary artery disease. Long-chain n-3 polyunsaturate deficiency may also contribute to depressive symptoms in alcoholism, multiple sclerosis, and postpartum depression. We postulate that adequate long-chain polyunsaturated fatty acids, particularly docosahexaenoic acid, may reduce the development of depression just as n-3 polyunsaturated fatty acids may reduce coronary artery disease.

Indirect evidence for nitric oxide involvement in multiple sclerosis by characterization of circulating antibodies directed against conjugated S-nitrosocysteine.

Boullerne AI, Petry KG, Meynard M, Geffard M INSERM U394 Neurobiologie integrative, Bordeaux, France.

J Neuroimmunol (Netherlands) Jul 1995, 60 (1-2) p117-24

Converging data suggest that nitric oxide (NO) production by cytokine-induced immune cells in demyelinating lesions is involved in multiple sclerosis (MS). High levels of NO may complex to suitable amino acids, causing an immune response against the formed neo-epitopes. By testing MS sera with chemically defined nitroso-amino acids conjugated to carrier protein in ELISA, we observed a significant antibody reaction against the S-nitroso-cysteine epitope. The MS antibody response was exclusively of IgM isotype with an avidity of 8 x 10(-7) M. Sera of all clinical MS forms showed a significantly elevated antibody titer versus sera from healthy subjects or from patients affected with other neurological and autoimmune diseases. The detection of circulating antibodies to a conjugated S-nitroso-cysteine epitope provides indirect evidence for NO involvement in MS.

Isoprenoid (CoQ10) biosynthesis in multiple sclerosis.

Steen G, Axelsson H, Bowallius M, Holthuis N, Molander BM

Acta Neurol Scand (Denmark) Sep 1985, 72 (3) p328-35

Recently discovered metabolites in urine have suggested a defect of isoprenoid metabolism in multiple sclerosis. Lymphocyte HMG-CoA reductase was found unaffected however, and so was lymphocyte biosynthesis of geraniol, farnesol and squalene from mevalonolactone. The level of dolichol in white matter of an MS brain was similar to that of a control sample. Serum ubiquinone, on the other hand, was decreased in multiple sclerosis. Ubiquinone in serum was both age-dependent and related to serum cholesterol. Active as well as stable MS displayed

a decreased level of serum ubiquinone, and a reduced ubiquinone-cholesterol ratio. These results are compatible with a deficient ubiquinone biosynthesis in multiple sclerosis.

Abnormality of fatty acid composition of plasma lipid in multiple sclerosis

Sato S, Shirakawa K, Tsubaki T, Sakuragawa N

Brain Nerve (Tokyo) (Japan), 1979, 31/8 (797-801)

It has been reported that the composition of fatty acid is abnormal in the blood of European patients with multiple sclerosis (MS). The purpose of the present paper is to confirm such an abnormality in Japanese MS. The level of linoleic acid was decreased significantly in active stage at seven relapses in four cases of MS. While the level of plasma linoleic acid was decreased the non-essential fatty acids oleate and palmitate showed significant increase in these relapses. In thirteen patients with MS who were in remission, the level of arachidonic acid was decreased. Clinical courses were correlated to linoleic acid levels in four cases of active MS. The level of linoleic acid was decreased at each relapse and returned to normal in remission.

The pineal and regulation of fibrosis: pinealectomy as a model of primary biliary cirrhosis: Roles of melatonin and prostaglandins in fibrosis and regulation of T lymphocytes

Cunnane SC, Manku MS, Horrobin DF

Med. Hypotheses (England), 1979, 5/4 (403-414)

Pinealectomy leads to increased formation of fibrous tissue in the abdominal cavity, increased skin pigmentation and elevated cholesterol and alkaline phosphatase levels. It also leads to reduced formation and/or action of prostaglandin (PG) E1 and thromboxane (TX) A2. PGE1 plays an important role in enhancing function of T suppressor lymphocytes. In primary biliary cirrhosis there are increased skin pigmentation, hepatic fibrosis, elevated cholesterol and alkaline phosphatase levels, defective T lymphocytes and hyperactive B lymphocytes. Primary biliary cirrhosis may be a pineal deficiency disease. Serotonin is important in the pineal and the serotonin antagonist methysergide may cause retroperitoneal fibrosis by interfering with pineal function. These is a good deal of other evidence which suggests that melatonin PGE1 and TXA2 are important in the regulation of fibrosis in other situations such as 'collagen' diseases, lithium-induced fibrosis and cardiomyopathies. This suggests that enhancement of formation of PGE1 and of TXA2 may be of value in diseases associated with excess fibrosis and defective T suppressor cell function. PGE1 levels may be raised by zinc, penicillin, penicillamine and essential fatty acids. TXA2 levels may be raised by low dose colchicine. These new approaches to treatment may prove safer and more effective than existing ones. They may be of value in disorders such as cardiomyopathy, Hodgkin's disease and other

lymphomas, multiple sclerosis, Crohn's disease, atopy and other diseases in which defective T cell function is suspected.

Fatty acid patterns of serum lipids in multiple sclerosis and other diseases

Love W.C.; Reynolds M.; Cashel A.; Callaghan N. Clin. Biochem. Lab., Trinity Coll., Dublin Ireland

Biochem.Soc.Trans. (England), 1973, 1/1 (141-143)

The fatty acid composition of phosphatidylcholines (lecithins) from the brains of patients with multiple sclerosis is altered from that of normal brain. Even in non plaque areas there was an increase in the saturated and a decrease in the unsaturated fatty acids. When the fatty acid composition of serum total lipid extracts was analysed a similar observation was made, with the major decrease occurring in the linoleate fraction. The decrease in linoleate in multiple sclerosis was most marked in the cholesterol linoleate fraction, and was also observed in the lipids of erythrocytes and platelets from patients with this disease. These findings led to the reasonable speculation that the decrease in serum linoleate in the active phase of multiple sclerosis may be due to a dietary deficiency or failure to absorb this fatty acid. The linoleate content of serum lipids is decreased in a variety of acute illnesses and is not specific for multiple sclerosis or other neurological disease. However, attention is drawn to the similarity of the fatty acid pattern of serum lipids in acute illness to that of essential fatty acid deficiency. This phenomenon bears further investigation to see whether the decrease in linoleate content precedes or is a consequence of the illness, and draws attention to the possibility that requirements or metabolism of essential fatty acids may be altered significantly by a large variety of acute illnesses.

Magnesium concentration in plasma and erythrocytes in MS

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Acta Neurologica Scandinavica (Denmark), 1995, 92/1 (109-111)

There are few reports of Mg in MS and none dealing with Mg content in erythrocytes. Mg concentration was determined in serum and in erythrocytes with the help of a BIOTROL Magnesium Calmagite colorimetric method (average sensitivity: 0.194 A per mmol/I) and a Hitachi autoanalyzer in 24 MS patients (7 men and 17 women, age 29-60; 37 years on average with the duration of the disease: 3-19; 11 years on average, at clinical disability stages according to the Kurtzke scale: 1-7; 3.2 on average, in remission stage. A statistically significant decrease ($p < 0.001$) of Mg concentration in erythrocytes and no changes in plasma of MS patients were found. The results obtained suggest the presence of changes in membrane of erythrocytes which could be connected with their shorter life and with affection of their function.

Magnesium concentration in brains from multiple sclerosis patients

Yasui M, Yase Y, Ando K, Adachi K, Mukoyama M, Ohsugi K Division of Neurological Diseases, Wakayama Medical College, Japan.

Acta Neurol. Scand. (Denmark), 1990, 81/3 (197-200)

Magnesium(Mg) concentrations were studied in the brains of 4 patients with definite multiple sclerosis (MS) and 5 controls. The magnesium contents were determined by inductively coupled plasma emission spectrometry in autopsy samples taken from 26 sites of central nervous system tissues, and visceral organs such as liver, spleen, kidney, heart and lung. The average Mg content in the CNS tissues, as well as visceral organs except for spleen, of MS patients showed a significantly lower value than that seen in control cases. The most marked reduction of Mg content was observed in CNS white matter including demyelinated plaques of MS samples. Whether or not these significantly lower Mg contents found in CNS and visceral organs of MS patients may play an essential role in the demyelinating process remain unclear, requiring further studies on MS pathogenesis from the point of metal metabolism.

Zinc, copper and magnesium concentration in serum and CSF of patients with neurological disorders

Kapaki E, Segditsa J, Papageorgiou C Department of Neurology, Aeginition University Hospital, Athens, Greece.

Acta Neurol. Scand. (Denmark), 1989, 79/5 (373-378)

Zinc (Zn), copper (Cu) and magnesium(Mg) concentrations in cerebrospinal fluid (CSF) and serum were determined with atomic absorption spectrophotometry in 74 patients suffering from various neurological diseases, and in 28 healthy controls. Increased CSF zinc levels were found in the group of peripheral nervous system diseases ($P < 0.01$) and in the cases of different neurological syndromes with increased CSF protein concentration ($P < 0.001$). Increased CSF and serum copper levels were found in the cases with increased CSF protein levels ($P < 0.05$). It is probable that damaged blood-brain-barrier (BBB) permits the passage of the trace elements Zn, Cu and of Mg into the subarachnoid space. Decreased serum Cu levels ($P < 0.01$) were found in the group of multiple sclerosis (MS). The findings are correlated to those of previous communications.

Evaluation of a nutrition education programme for people with multiple sclerosis

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J. Hum. Nutr. Diet. (United Kingdom), 1993, 6/2 (131-147)

A nutrition education programme was designed specifically to meet the needs of people with multiple sclerosis (MS) and implemented in five self-help groups. The programme was evaluated by means of two 7-day weighed food and drink

records carried out before and after the programme, by an attitude questionnaire and subjectively by the dietitians and participants. Although the diets of the 48 participants were good before the programme, there were significant improvements in the mean intakes of added sugar, saturated fatty acids, N-3 PUFA, P/S ratio and energy from N-3 PUFA in both males and females. RNIs for all mean intakes of vitamins and minerals were met by males and females both before and after the programme and intakes were generally better than mean values for the British adult population. Seventy-five per cent of the group took food supplements before the programme and 65% after. The diets of those people who took supplements before the programme were better, compared with those who did not, in terms of fibre, Vitamin-C, saturated fatty acids, N-3 and N-6 PUFAs. The supplemented group also made more significant changes in their diets compared with the unsupplemented group. Attitudes towards diet were found to be positive both before and after the programme. Dietitians and participants subjectively evaluated the programme and their suggested alterations were incorporated into the programme.

On the causes of multiple sclerosis

Hutter C City Hospital, Nottingham, UK.

Med. Hypotheses (United Kingdom), 1993, 41/2 (93-96)

Evidence on aetiology in multiple sclerosis suggests that the prevalence depends on the interaction of two factors, diet and exposure to visible sunlight. The dietary features which may be beneficial include supplementation with fish oils, avoidance of saturated fats, and the associated intake of antioxidants with unsaturated fatty acids. Inhibition, by antioxidants, of the enzyme lipoxygenase inhibits leukotriene synthesis, and the presence of fish oils leads to the production of leukotrienes with less inflammatory properties. This is of particular importance in the retina where leukotrienes might be the underlying cause of retrobulbar neuritis. The antioxidant properties of vitamin A may also lead to inhibition of leukotriene synthesis. Visible solar radiation could be of benefit therefore by releasing vitamin A from visual pigment rhodopsin. The interaction ot these two factors may explain the epidemiological observations on the prevalence of multiple sclerosis.

Lipids and neurological diseases.

Marshall BH

Med Hypotheses 1991 Mar;34(3):272-4

Neurological diseases, such as multiple sclerosis (MS), Sjogren-Larsson syndrome, Reye's syndrome, and Refsum's syndrome (herediopathica atactica polyneuroformis), and many others afflict millions of persons yearly and have no successful treatment available. A common aspect of these diseases appears to be a lipid imbalance involving the essential fatty acids (EFA), linoleic and linolenic, and trace fatty acids which result from faulty lipid metabolism. It is proposed that

treatments for these diseases should be sought through diet and metabolic enzymes rather than drugs.

Essential fatty acid and lipid profiles in plasma and erythrocytes in patients with multiple sclerosis.

Cunnane SC, Ho SY, Dore-Duffy P, Ells KR, Horrobin DF Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Canada.

Am J Clin Nutr (United States) Oct 1989, 50 (4) p801-6

This study was conducted to investigate the possible differences in erythrocyte lipid composition, which might account for the previously reported increase in erythrocyte membrane zinc levels in patients with multiple sclerosis (MS). Compared with healthy control subjects, plasma lipids in patients with MS contained less sphingomyelin but more phosphatidylserine and the cholesterol-phospholipid ratio was 42% higher in the plasma from MS patients (p less than 0.01). In erythrocytes from MS patients, phosphatidylinositol was lower and erythrocyte cholesterol per milligram protein was significantly lower than concentrations in healthy control subjects (p less than 0.01). Among the long-chain fatty acids, the omega-3 fatty acids were lower in plasma from MS patients and linoleic acid was lower in erythrocyte ghosts from MS patients (p less than 0.01). We conclude that altered levels of cholesterol in plasma and erythrocytes from MS patients may contribute to increased erythrocyte-membrane Zn in MS patients. It cannot be stated with certainty whether the altered fatty acid profiles in MS patients were a function of the disease or of altered fatty acid intake.

Plasma lipids and their fatty acid composition in multiple sclerosis.

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Acta Neurol Scand (Denmark) Aug 1988, 78 (2) p152-7

We report an extensive study of the plasma lipid profile and fatty acid composition in 61 multiple sclerosis (MS) patients compared with 61 normal subjects. The main abnormality in the MS was a reduction in the proportion of linoleic and arachidonic acids mostly evident in the HDL and in the cholesteryl esters fraction, with a compensatory increase in saturated acids. The fatty acid abnormalities correlated with the duration of the disease and the degree of disability. Thus, in the MS patients studied there as a deficiency in essential fatty acids, although this metabolic abnormality does not seem specific to MS.

The effect of nutritional counselling on diet and plasma EFA status in multiple sclerosis patients over 3 years.

Fitzgerald G; Harbige LS; Forti A; Crawford MA ARMS Research Unit, Central Middlesex Hospital, Acton, London, UK.

Hum Nutr Appl Nutr 1987 Oct;41(5):297-310

The dietary intake of 83 people with multiple sclerosis (MS) was assessed by the 7-day weighed intake method prior to dietary advice and at 6-monthly intervals thereafter up to 36 months. The P:S ratio of the diet increased from an initial value of 0.8 to 1.5 after 6 months and 1.34 at 36 months. Biochemical investigation of plasma essential fatty acid (EFA) status specifically linoleic, eicosapentanoic and docosahexanoic acids showed significant correlations with diet. Concurrent 6-monthly neurological and physiotherapy assessments were also carried out, the neurological results are discussed in relation to a nutrient scoring system.

Essential fatty acids in the serum and cerebrospinal fluid of multiple sclerosis patients.

Neu IS

Acta Neurol Scand (Denmark) Mar 1983, 67 (3) p151-63

Statistical evaluation of essential fatty acids (determined by gas chromatography) in the serum and cerebrospinal fluid of patients with definite MS and acute CCT showed marked differences as compared to healthy subjects. It was also evident that the decrease of essential fatty acids in MS patients differed from that of CCT patients. Whereas the fatty acid levels in the serum of MS patients revealed only minor differences as compared to the controls and CCT patients, MS patients did show a clear decrease, especially of linoleic and arachidonic acids, in the CSF. This difference was most pronounced in cholesterol esters in the CSF. One absorption study with safflower oil demonstrated normal enteral absorption of essential fatty acids and the ability to cross the blood-CSF barrier.

Multiple sclerosis: the rational basis for treatment with colchicine and evening primrose oil.

Horrobin DF

Med Hypotheses (England) Mar 1979, 5 (3) p365-78

Multiple sclerosis (MS) is a disease with no known treatment. In view of this and of its distressing nature patients are attracted by any new concepts. As a reaction to this neurologists are sometimes excessively sceptical and fail to consider new approaches seriously. Recent attempts have been made to treat multiple sclerosis with polyunsaturated fatty acids and with colchicine. This approach is not arbitrary and is firmly grounded in fundamental basic scientific concepts. In patients with multiple sclerosis there is evidence of both an abnormality in essential fatty acid metabolism and an abnormality in lymphocyte function. It is now apparent that the fatty acid abnormality may cause the lymphocyte abnormality and that both may be improved by dietary manipulation. There is also evidence that the demyelination may be associated with recurrent inflammatory episodes and with entry of calcium into the cytoplasm. In vitro colchicine has

been shown to have actions compatible with regulation of cytoplasmic calcium and in two diseases characterised by intermittent inflammatory episodes (Behcets syndrome and familial Mediterranean fever) it has been found to prevent or to reduce the severity of such episodes. Preliminary results suggest that combined therapy with evening primrose oil and colchicine may be of considerable value.

Red blood cell and adipose tissue fatty acids in mild inactive multiple sclerosis.

Nightingale S, Woo E, Smith AD, French JM, Gale MM, Sinclair HM, Bates D, Shaw DA Department of Neurology, Royal Victoria Infirmary, Newcastle upon Tyne.

Acta Neurol Scand (Denmark) Jul 1990, 82 (1) p43-50

The fatty acid profiles of phosphatidyl ethanolamine (PE) and phosphatidyl choline (PC) of the red blood cells of 30 patients with mild inactive multiple sclerosis (MS) and 30 healthy controls were studied by gas chromatography. The groups were well matched for factors likely to influence tissue lipid levels, including diet. The MS patients showed a significant reduction in PE eicosapentaenoic acid ($p = 0.009$) especially in women, and an increase in both PE dihomo-gamma-linolenic acid ($p = 0.004$) and PC stearic acid ($p = 0.04$). No reduction in linoleic acid was observed in either the PC or PE fractions of the MS subjects. A similar study of the fatty acid profile in adipose tissue in 26 MS and 35 healthy controls found no detectable eicosapentaenoic acid in either group. However, whereas docosahexaenoic acid was not detectable in any MS patient, 40% of the controls had measurable levels varying from to 0.1 to 0.3% of total estimated fatty acid ($p = 0.0003$). No reduction in linoleic acid in MS subjects was observed. Supplementation with oral fish body oil demonstrated that n-3 fatty acids were incorporated into red blood cells over 5 weeks and this occurred equally in MS and controls. The effects of oral supplementation on adipose tissue were studied after 1 and 2 years. Whereas many fatty acids such as linoleic acid were raised at 1 year, but did not rise subsequently, eicosapentaenoic acid and docosahexaenoic acid continued to rise through the 2-year period.

The nutritional regulation of T lymphocyte function.

Horrobin DF, Manku MS, Oka M, Morgan RO, Cunnane SC, Ally AI, Ghayur T, Schweitzer M, Karmali RA

Med Hypotheses (England) Sep 1979, 5 (9) p969-85

Prostaglandin (PG) E1 plays a major role in the regulation of thymus development and T lymphocyte function and the evidence for this is reviewed. The production of PGE1 is dependent on nutritional factors with linoleic acid, gamma-linolenic acid, pyridoxine, zinc and Vitamin-C playing key roles. Inadequate intake of any one of these will lead to inadequate PGE1 formation and defective T lymphocyte function. Megadoses of any one are likely to be only minimally effective in the absence of adequate intakes of the others. By careful attention to diet it should be

possible to activate T lymphocyte function in the large number of diseases including rheumatoid arthritis, various auto-immune diseases, multiple sclerosis, and cancer in which such function is defective. It is possible that T lymphocytes may require both endogenous and exogenous PGE1 in order to function adequately. It is therefore of particular interest that many cancer cells and virally infected cells are unable to make PGE1 because they cannot convert linoleic acid to gamma-linolenic acid. The direct provision of gamma-linolenic or dihomo-gammalinolenic acids in these situations is worthy of full investigation.

Effect of prolonged ingestion of gamma-linolenate by MS patients.

Field EJ, Joyce G

Eur Neurol (Switzerland) 1978, 17 (2) p67-76

The absolute electrophoretic mobility of erythrocytes from MS patients is reduced in the presence of 0.08 mg/ml of linoleic or arachidonic acid, whilst that of normal or other neurological disease patients is increased in the presence of these acids. When an MS patient ingests gamma-linolenate (in capsule form equivalent to 413.4 mg of gamma-linolenic acid and 2.664 g of linoleic acid per day) the reaction of MS erythrocytes begins to change. After 3 or 4 months the reaction becomes normal with arachidonic acid (i.e. mobility is speeded up) and 2 months or so later this occurs also with linoleic acid. Very prolonged administration of gamma-linolenate leads to a markedly increased sensitivity to the effect of prostaglandins (PGE2) on RBC mobility. The observations are interpreted to mean the induction of a biochemical-biophysical change in the membranes, and the significance of this in the aetiology and treatment of multiple sclerosis is discussed.

Experimental and clinical studies on dysregulation of Magnesium metabolism and the aetiopathogenesis of multiple sclerosis.

Yasui M, Ota K Division of Neurological Diseases, Wakayama Medical College, Japan.

Magnes Res (England) Dec 1992, 5 (4) p295-302

The proposed aetiologies of multiple sclerosis (MS) have included immunological mechanisms, genetic factors, virus infection and direct or indirect action of minerals and/or metals. The processes of these aetiologies have implicated magnesium. Magnesium and zinc have been shown to be decreased in central nervous system (CNS) tissues of MS patients, especially tissues such as white matter where pathological changes have been observed. The calcium content of white matter has also been found to be decreased in MS patients. The interactions of minerals and/or metals such as calcium, magnesium, aluminium and zinc have also been evaluated in CNS tissues of experimental animal models. These data suggest that these elements are regulated by pooling of minerals and/or metals in bones. Biological actions of magnesium may affect the maintenance and function of nerve cells as well as the proliferation and synthesis of lymphocytes. A

magnesium deficit may induce dysfunction of nerve cells or lymphocytes directly and/or indirectly, and thus magnesium depletion may be implicated in the aetiology of MS. The action of zinc helps to prevent virus infection, and zinc deficiency in CNS tissues of MS patients may also be relevant to its aetiology. Magnesium interacts with other minerals and/or metals such as calcium, zinc and aluminium in biological systems, affecting the immune system and influencing the content of these elements in CNS tissues. Because of these interactions, a magnesium deficit could also be a risk factor in the aetiology of MS.

Multiple sclerosis and neurotransmission

Ali Qureshi G.; Halawa A.; Baig S.; Siden A.
Clinical Research Center, Dept. Clin. Neuroscience Family Med., Huddinge University Hospital, S-141 57 Stockholm Sweden
Biogenic Amines (Netherlands), 1996, 12/5 (353-376)

In this study, the role of excitatory amino acids (EAA), nitrite (metabolite of nitric oxide), vitamin B12, homocysteine (HC), monoamines, and neuropeptides such as cholecystokinin (CCK) and neuropeptide Y in multiple sclerosis (MS) is defined on the basis of accumulated results obtained in cerebrospinal fluid from 47 MS patients. These results were compared with 25 healthy subjects. These results showed the significant increase of free radical NO, arginine, tryptophan, noradrenaline and HC, and decrease in the levels of Apartate, glutamate, dopamine, vitamin B12, CCK-4 and CCK-8 in MS patients. From these results, the role of NO, HC and deficiency of vitamin B12 are considered as some of the factors attributing to the degeneration of MS.

[Visual, auditory and somatosensory potentials in the diagnosis of vitamin B12 deficiency]

Cheliout-Heraut F, Durand MC, Desterbecq E, Dizien O, de Lattre J
Service d'explorations fonctionnelles, hopital Raymond Poincare, Garches, France.
Neurophysiol Clin 1997;27(1):59-65

We describe visual, brain stem auditory, and somatosensory evoked (VEP, BAEP, SEP) in a 49-year old male patient presenting with subacute degeneration of the spinal cord due to vitamin B12 deficiency. Neurological signs included tetraplegia with a C4-C5 spinal cord compression that was unchanged after surgical decompression. Before treatment, the duration of the bilateral VEP was slightly increased, though their amplitude and morphology were not modified. BAEP were normal. However, abnormalities of SEP with loss of cortical potentials were noticed. Two months after initiation of the treatment, both VEP and SEP recorded in response to median nerve stimulation had improved, but there was still no cortical response to tibial nerve stimulation. Eighteen months later, VEP were normal and recovery of SEP in response to tibial nerve stimulation was observed; however, alterations of peripheral sensory and motor action potentials were still

present. These findings are in good agreement with previously reported pathological changes in patients presenting with subacute combined degeneration. Similar abnormalities have been described in patients with multiple sclerosis. Evoked potentials in this case proved to be useful for the diagnosis and the evaluation of the efficacy of the treatment. These findings also suggest that demyelination of the posterior part of the spinal cord and peripheral axonal degeneration might be the main pathological changes related to vitamin B12 deficiency. The former, but not like the latter, were clearly responsive to the treatment.

Folate, vitamin B12, and neuropsychiatric disorders.

Bottiglieri T
Kimberly H. Courtwright and Joseph W. Summers Institute of Metabolic Disease, Baylor University Medical Center, Dallas, Texas, USA.
Nutr Rev (United States) Dec 1996, 54 (12) p382-90

Folate and vitamin B12 are required both in the methylation of homocysteine to methionine and in the synthesis of S-adenosylmethionine. S-adenosylmethionine is involved in numerous methylation reactions involving proteins, phospholipids, DNA, and neurotransmitter metabolism. Both folate and vitamin B12 deficiency may cause similar neurologic and psychiatric disturbances including depression, dementia, and a demyelinating myelopathy. A current theory proposes that a defect in methylation processes is central to the biochemical basis of the neuropsychiatry of these vitamin deficiencies. Folate deficiency may specifically affect central monoamine metabolism and aggravate depressive disorders. In addition, the neurotoxic effects of homocysteine may also play a role in the neurologic and psychiatric disturbances that are associated with folate and vitamin B12 deficiency.

1,25-dihydroxyvitamin D3 reversibly blocks the progression of relapsing encephalomyelitis, a model of multiple sclerosis

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Proceedings of the National Academy of Sciences of the United States of America (USA), 1996, 93/15 (7861-7864)

Experimental autoimmune encephalomyelitis (EAE) is an autoimmune disease believed to be a model for the human disease multiple sclerosis (MS). Induced by immunizing B10.PL mice with myelin basic protein (MBP). EAE was completely prevented by the administration of 1,25-dihydroxyvitamin D3 (1,25- (OH)2D3). 1,25-(OH)2D3 could also prevent the progression of EAE when administered at the appearance of the first disability symptoms. Withdrawal of 1,25-(OH)2D3

resulted in a resumption of the progression of EAE. Thus, the block by 1,25-(OH)2D3 is reversible. A deficiency of vitamin D resulted in an increased susceptibility to EAE. Thus, 1,25-(OH)2D3 or its analogs are potentially important for treatment of MS.

Measurement of low-molecular-weight antioxidants, uric acid, tyrosine and tryptophan in plaques and white matter from patients with multiple sclerosis.

Langemann H, Kabiersch A, Newcombe J
Department of Research, Cantonal Hospital Basel, Switzerland.
Eur Neurol (Switzerland) 1992, 32 (5) p248-52

The levels of the antioxidants ascorbic acid, cysteine, reduced glutathione and alpha-tocopherol, of the free-radical marker uric acid and of the amino acids tyrosine and tryptophan were measured by means of high-pressure liquid chromatography in plaques, adjacent white matter and distant white matter from patients with multiple sclerosis, and in central nervous system tissue from patients without neurological diseases. Cholesterol and DNA were also determined, to check demyelination and cellularity. Uric acid was increased and glutathione correspondingly decreased in plaques; alpha-tocopherol was lowest in plaques and highest in distant white matter in all cases. Ascorbic acid, cysteine, tyrosine and tryptophan were not significantly changed in any tissue. The results provide evidence supporting the involvement of free radicals in multiple sclerosis.

Clinical trials of unsaturated fatty acids in multiple sclerosis

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IRCS Med. Sci. (England), 1981, 9/12 (1081)

The membrane of MS-RBC (multiple sclerosis-erythrocytes) is different from non-MS. Until now it was believed that 6-8 months treatment with gamma-linolenate converted their abnormal properties into normal, as judged by electrophoretic measurements in the presence of LA (linoleic acid) and AA (arachidonic acid). Further experimentation has shown however, such conversion to non-MS type is delayed until 21-24 months after gamma-linolenate feeding, when low doses of LA and AA begin to have the same effect on mobility as they do in normal cells. Thus any clinical trial of PUFA should begin about 2 years after it is instituted - not concluded, as at present. This may account for the relative success of Swank's dietary treatment which spans over 20 years. The long term requirement for essential fatty acids (EFA) to restore membrane normality in MS must be taken into account in planning therapeutic trials.

Dietary polyunsaturated fatty acids and depression: When cholesterol does not satisfy

Hibbeln JR, Salem N Jr
Laboratory of Membrane Biophysics and Biochemistry, DICBR, National Institute of Alcohol Abuse and Alcoholism, Rockville, MD 20852, USA.
American Journal of Clinical Nutrition (USA), 1995, 62/1 (1-9)

Recent studies have both offered and contested the proposition that lowering plasma cholesterol by diet and medications increases suicide, homicide, and depression. Significant confounding factors include the quantity and distribution of dietary n-6 and n-3 polyunsaturated essential fatty acids that influence serum lipids and alter the biophysical and biochemical properties of cell membranes. Epidemiological studies in various countries and in the United States in the last century suggest that decreased n-3 fatty acid consumption correlates with increasing rates of depression. This is consistent with a well-established positive correlation between depression and coronary artery disease. Long-chain n-3 polyunsaturate deficiency may also contribute to depressive symptoms in alcoholism, multiple sclerosis, and postpartum depression. We postulate that adequate long-chain polyunsaturated fatty acids, particularly docosahexaenoic acid, may reduce the development of depression just as n-3 polyunsaturated fatty acids may reduce coronary artery disease.

Indirect evidence for nitric oxide involvement in multiple sclerosis by characterization of circulating antibodies directed against conjugated S-nitrosocysteine.

Boullerne AI, Petry KG, Meynard M, Geffard M
INSERM U394 Neurobiologie integrative, Bordeaux, France.
J Neuroimmunol (Netherlands) Jul 1995, 60 (1-2) p117-24

Converging data suggest that nitric oxide (NO) production by cytokine-induced immune cells in demyelinating lesions is involved in multiple sclerosis (MS). High levels of NO may complex to suitable amino acids, causing an immune response against the formed neo-epitopes. By testing MS sera with chemically defined nitroso-amino acids conjugated to carrier protein in ELISA, we observed a significant antibody reaction against the S-nitroso-cysteine epitope. The MS antibody response was exclusively of IgM isotype with an avidity of 8 x 10(-7) M. Sera of all clinical MS forms showed a significantly elevated antibody titer versus sera from healthy subjects or from patients affected with other neurological and autoimmune diseases. The detection of circulating antibodies to a conjugated S-nitroso-cysteine epitope provides indirect evidence for NO involvement in MS.

Isoprenoid (coQ10) biosynthesis in multiple sclerosis.

Steen G, Axelsson H, Bowallius M, Holthuis N, Molander BM
Acta Neurol Scand (Denmark) Sep 1985, 72 (3) p328-35

Recently discovered metabolites in urine have suggested a defect of isoprenoid metabolism in multiple sclerosis. Lymphocyte HMG-CoA reductase was found unaffected however, and so was lymphocyte biosynthesis of geraniol, farnesol and squalene from mevalonolactone. The level of dolichol in white matter of an MS brain was similar to that of a control sample. Serum ubiquinone, on the other hand, was decreased in multiple sclerosis. Ubiquinone in serum was both age-dependent and related to serum cholesterol. Active as well as stable MS displayed a decreased level of serum ubiquinone, and a reduced ubiquinone-cholesterol ratio. These results are compatible with a deficient ubiquinone biosynthesis in multiple sclerosis.

Abnormality of fatty acid composition of plasma lipid in multiple sclerosis

Sato S, Shirakawa K, Tsubaki T, Sakuragawa N
Brain Nerve (Tokyo) (Japan), 1979, 31/8 (797-801)

It has been reported that the composition of fatty acid is abnormal in the blood of European patients with multiple sclerosis (MS). The purpose of the present paper is to confirm such an abnormality in Japanese MS. The level of linoleic acid was decreased significantly in active stage at seven relapses in four cases of MS. While the level of plasma linoleic acid was decreased the non-essential fatty acids oleate and palmitate showed significant increase in these relapses. In thirteen patients with MS who were in remission, the level of arachidonic acid was decreased. Clinical courses were correlated to linoleic acid levels in four cases of active MS. The level of linoleic acid was decreased at each relapse and returned to normal in remission.

The pineal and regulation of fibrosis: pinealectomy as a model of primary biliary cirrhosis: Roles of melatonin and prostaglandins in fibrosis and regulation of T lymphocytes

Cunnane SC, Manku MS, Horrobin DF
Med. Hypotheses (England), 1979, 5/4 (403-414)

Pinealectomy leads to increased formation of fibrous tissue in the abdominal cavity, increased skin pigmentation and elevated cholesterol and alkaline phosphatase levels. It also leads to reduced formation and/or action of prostaglandin (PG) E1 and thromboxane (TX) A2. PGE1 plays an important role

in enhancing function of T suppressor lymphocytes. In primary biliary cirrhosis there are increased skin pigmentation, hepatic fibrosis, elevated cholesterol and alkaline phosphatase levels, defective T lymphocytes and hyperactive B lymphocytes. Primary biliary cirrhosis may be a pineal deficiency disease. Serotonin is important in the pineal and the serotonin antagonist methysergide may cause retroperitoneal fibrosis by interfering with pineal function. These is a good deal of other evidence which suggests that melatonin PGE1 and TXA2 are important in the regulation of fibrosis in other situations such as 'collagen' diseases, lithium-induced fibrosis and cardiomyopathies. This suggests that enhancement of formation of PGE1 and of TXA2 may be of value in diseases associated with excess fibrosis and defective T suppressor cell function. PGE1 levels may be raised by zinc, penicillin, penicillamine and essential fatty acids. TXA2 levels may be raised by low dose colchicine. These new approaches to treatment may prove safer and more effective than existing ones. They may be of value in disorders such as cardiomyopathy, Hodgkin's disease and other lymphomas, multiple sclerosis, Crohn's disease, atopy and other diseases in which defective T cell function is suspected.

Fatty acid patterns of serum lipids in multiple sclerosis and other diseases

Love W.C.; Reynolds M.; Cashel A.; Callaghan N.
Clin. Biochem. Lab., Trinity Coll., Dublin Ireland
Biochem.Soc.Trans. (England), 1973, 1/1 (141-143)

The fatty acid composition of phosphatidylcholines (lecithins) from the brains of patients with multiple sclerosis is altered from that of normal brain. Even in non plaque areas there was an increase in the saturated and a decrease in the unsaturated fatty acids. When the fatty acid composition of serum total lipid extracts was analysed a similar observation was made, with the major decrease occurring in the linoleate fraction. The decrease in linoleate in multiple sclerosis was most marked in the cholesterol linoleate fraction, and was also observed in the lipids of erythrocytes and platelets from patients with this disease. These findings led to the reasonable speculation that the decrease in serum linoleate in the active phase of multiple sclerosis may be due to a dietary deficiency or failure to absorb this fatty acid. The linoleate content of serum lipids is decreased in a variety of acute illnesses and is not specific for multiple sclerosis or other neurological disease. However, attention is drawn to the similarity of the fatty acid pattern of serum lipids in acute illness to that of essential fatty acid deficiency. This phenomenon bears further investigation to see whether the decrease in linoleate content precedes or is a consequence of the illness, and draws attention to the possibility that requirements or metabolism of essential fatty acids may be altered significantly by a large variety of acute illnesses.

Magnesium concentration in plasma and erythrocytes in MS

Stelmasiak Z, Solski J, Jakubowska B
Department of Clinical Analytics, School of Medicine, Lublin, Poland.
Acta Neurologica Scandinavica (Denmark), 1995, 92/1 (109-111)

There are few reports of Mg in MS and none dealing with Mg content in erythrocytes. Mg concentration was determined in serum and in erythrocytes with the help of a BIOTROL Magnesium Calmagite colorimetric method (average sensitivity: 0.194 A per mmol/I) and a Hitachi autoanalyzer in 24 MS patients (7 men and 17 women, age 29-60; 37 years on average with the duration of the disease: 3-19; 11 years on average, at clinical disability stages according to the Kurtzke scale: 1-7; 3.2 on average, in remission stage. A statistically significant decrease ($p < 0.001$) of Mg concentration in erythrocytes and no changes in plasma of MS patients were found. The results obtained suggest the presence of changes in membrane of erythrocytes which could be connected with their shorter life and with affection of their function.

Comparative findings on serum IMg2+ of normal and diseased human subjects with the NOVA and KONE ISE's for Mg2+

Altura BT, Bertschat F, Jeremias A, Ising H, Altura BM
Department of Physiology, State University of New York, Health Science Center at Brooklyn 11203.
Scand J Clin Lab Invest Suppl 1994;217:77-81

It is clear now that although different ionophores for ionized Mg (Img2+) have been designed by several groups, each of these has a distinctly different K(MgCa). In view of this, it is important to determine whether each of these ion selective electrodes (ISE's) yield identical results for IMg2+ in sera from healthy and diseased humans. Using such an approach, we determined, in a blinded-and random manner, IMg2+ with both the NOVA and KONE ISE's for IMg2+ in two independent laboratories. No significant differences were found either for sera from healthy human volunteers or diseased patients. We did, however, note several interesting findings: 1. randomly, selected hospitalized patients exhibit a much higher incidence of abnormalities for IMg2+ (57-71%) than that noted previously for total Mg (TMg) measurements; and 2. coronary heart disease, rectal cancer and multiple sclerosis patients exhibit extracellular deficits in ionized free Mg.

Magnesium concentration in brains from multiple sclerosis patients

Yasui M, Yase Y, Ando K, Adachi K, Mukoyama M, Ohsugi K
Division of Neurological Diseases, Wakayama Medical College, Japan.
Acta Neurol. Scand. (Denmark), 1990, 81/3 (197-200)

Magnesium (Mg) concentrations were studied in the brains of 4 patients with definite multiple sclerosis (MS) and 5 controls. The magnesium contents were determined by inductively coupled plasma emission spectrometry in autopsy samples taken from 26 sites of central nervous system tissues, and visceral organs such as liver, spleen, kidney, heart and lung. The average Mg content in the CNS tissues, as well as visceral organs except for spleen, of MS patients showed a significantly lower value than that seen in control cases. The most marked reduction of Mg content was observed in CNS white matter including demyelinated plaques of MS samples. Whether or not these significantly lower Mg contents found in CNS and visceral organs of MS patients may play an essential role in the demyelinating process remain unclear, requiring further studies on MS pathogenesis from the point of metal metabolism.

Zinc, copper and magnesium concentration in serum and CSF of patients with neurological disorders

Kapaki E, Segditsa J, Papageorgiou C
Department of Neurology, Aeginition University Hospital, Athens, Greece.
Acta Neurol. Scand. (Denmark), 1989, 79/5 (373-378)

Zinc (Zn), copper (Cu) and magnesium (Mg) concentrations in cerebrospinal fluid (CSF) and serum were determined with atomic absorption spectrophotometry in 74 patients suffering from various neurological diseases, and in 28 healthy controls. Increased CSF zinc levels were found in the group of peripheral nervous system diseases ($P < 0.01$) and in the cases of different neurological syndromes with increased CSF protein concentration ($P < 0.001$). Increased CSF and serum copper levels were found in the cases with increased CSF protein levels ($P < 0.05$). It is probable that damaged blood-brain-barrier (BBB) permits the passage of the trace elements Zn, Cu and of Mg into the subarachnoid space. Decreased serum Cu levels ($P < 0.01$) were found in the group of multiple sclerosis (MS). The findings are correlated to those of previous communications.

Multiple sclerosis: Decreased relapse rate through dietary supplementation with calcium, magnesium and vitamin D

Goldberg P, Fleming MC, Picard EH
Med. Hypotheses (UK), 1986, 21/2 (193-200)

A group of young patients having multiple sclerosis was treated with dietary supplements containing calcium, magnesium and vitamin D for a period of one to two years. The experimental design employed self-pairing: the response of each patient was compared with his/her own case history as control. The number of exacerbations observed during the program was less than one half the number expected from case histories. No side effects were apparent. The dietary regimen may offer a new means of controlling the exacerbation rate in MS, at least for

younger patients. The results tend to support a theory of MS which states that calcium and magnesium are important in the development, structure and stability of myelin.

Evaluation of a nutrition education programme for people with multiple sclerosis

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J. Hum. Nutr. Diet. (United Kingdom), 1993, 6/2 (131-147)

A nutrition education programme was designed specifically to meet the needs of people with multiple sclerosis (MS) and implemented in five self-help groups. The programme was evaluated by means of two 7-day weighed food and drink records carried out before and after the programme, by an attitude questionnaire and subjectively by the dietitians and participants. Although the diets of the 48 participants were good before the programme, there were significant improvements in the mean intakes of added sugar, saturated fatty acids, N-3 PUFA, P/S ratio and energy from N-3 PUFA in both males and females. RNIs for all mean intakes of vitamins and minerals were met by males and females both before and after the programme and intakes were generally better than mean values for the British adult population. Seventy-five per cent of the group took food supplements before the programme and 65% after. The diets of those people who took supplements before the programme were better, compared with those who did not, in terms of fibre, Vitamin-C, saturated fatty acids, N-3 and N-6 PUFAs. The supplemented group also made more significant changes in their diets compared with the unsupplemented group. Attitudes towards diet were found to be positive both before and after the programme. Dietitians and participants subjectively evaluated the programme and their suggested alterations were incorporated into the programme.

Multiple sclerosis: A diathesis?

Adlam J.P.
Italy
Gazz.Sanit. (Milano) (Italy), 1973, 22/1 (37-39)

The incidence of multiple sclerosis among predisposed subjects is higher in cold climates, and is compounded where trace metals, such as copper, selenium and cobalt, are lacking in the diet. The importance of trace elements in various metabolic processes is discussed, including the etiology of multiple sclerosis. Screening children, removing those at risk to warmer climates and further research into trace metal physiology are recommended.

Lipids and neurological diseases.

Marshall BH
Med Hypotheses 1991 Mar;34(3):272-4

Neurological diseases, such as multiple sclerosis (MS), Sjogren-Larsson syndrome, Reye's syndrome, and Refsum's syndrome (herediopathica atactica polyneuroformis), and many others afflict millions of persons yearly and have no successful treatment available. A common aspect of these diseases appears to be a lipid imbalance involving the essential fatty acids (EFA), linoleic and linolenic, and trace fatty acids which result from faulty lipid metabolism. It is proposed that treatments for these diseases should be sought through diet and metabolic enzymes rather than drugs.

Essential fatty acid and lipid profiles in plasma and erythrocytes in patients with multiple sclerosis.

Cunnane SC, Ho SY, Dore-Duffy P, Ells KR, Horrobin DF
Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Canada.
Am J Clin Nutr (United States) Oct 1989, 50 (4) p801-6

This study was conducted to investigate the possible differences in erythrocyte lipid composition, which might account for the previously reported increase in erythrocyte membrane zinc levels in patients with multiple sclerosis (MS). Compared with healthy control subjects, plasma lipids in patients with MS contained less sphingomyelin but more phosphatidylserine and the cholesterol-phospholipid ratio was 42% higher in the plasma from MS patients (p less than 0.01). In erythrocytes from MS patients, phosphatidylinositol was lower and erythrocyte cholesterol per milligram protein was significantly lower than concentrations in healthy control subjects (p less than 0.01). Among the long-chain fatty acids, the omega-3 fatty acids were lower in plasma from MS patients and linoleic acid was lower in erythrocyte ghosts from MS patients (p less than 0.01). We conclude that altered levels of cholesterol in plasma and erythrocytes from MS patients may contribute to increased erythrocyte-membrane Zn in MS patients. It cannot be stated with certainty whether the altered fatty acid profiles in MS patients were a function of the disease or of altered fatty acid intake.

Plasma lipids and their fatty acid composition in multiple sclerosis.

Navarro X, Segura R
Department of Physiology, Autonomous University of Barcelona, Spain.
Acta Neurol Scand (Denmark) Aug 1988, 78 (2) p152-7

We report an extensive study of the plasma lipid profile and fatty acid composition in 61 multiple sclerosis (MS) patients compared with 61 normal subjects. The main abnormality in the MS was a reduction in the proportion of linoleic and arachidonic acids mostly evident in the HDL and in the cholesteryl esters fraction, with a compensatory increase in saturated acids. The fatty acid abnormalities correlated with the duration of the disease and the degree of disability. Thus, in the MS patients studied there as a deficiency in essential fatty acids, although this metabolic abnormality does not seem specific to MS.

The effect of nutritional counselling on diet and plasma EFA status in multiple sclerosis patients over 3 years.

Fitzgerald G; Harbige LS; Forti A; Crawford MA
ARMS Research Unit, Central Middlesex Hospital, Acton, London, UK.
Hum Nutr Appl Nutr 1987 Oct;41(5):297-310

The dietary intake of 83 people with multiple sclerosis (MS) was assessed by the 7-day weighed intake method prior to dietary advice and at 6-monthly intervals thereafter up to 36 months. The P:S ratio of the diet increased from an initial value of 0.8 to 1.5 after 6 months and 1.34 at 36 months. Biochemical investigation of plasma essential fatty acid (EFA) status specifically linoleic, eicosapentanoic and docosahexanoic acids showed significant correlations with diet. Concurrent 6-monthly neurological and physiotherapy assessments were also carried out, the neurological results are discussed in relation to a nutrient scoring system.

[Metabolic aspects of multiple sclerosis]

Neu IS
Wien Med Wochenschr (Austria) Jan 31 1985, 135 (1-2) p20-2

According to the present opinion multiple sclerosis (MS) is caused by a concurreance of various factors. This predisposing factor seem to be related to a disturbance of the lipid- and fatty acid metabolism, characterized by decreased concentrations of polyunsaturated fatty acids (PUFA) and essential fatty acids (EFA) in the plasma, the blood cells, the cerebrospinal fluid (CSF) and white matter of the brain in patients with MS. A disturbed absorption of EFA could be excluded. Now the question arises whether there is a disturbed utilisation of EFA with the consequence of biochemical changes in myelin and blood cells. According to lipid-chemical and lipolytic enzymological studies a disturbance of the fatty acid elongation system as well as primary increased activation of the phospholipase A1 is conceivable. According to the demonstrated results the conception of a metabolic immunological caused generalised defect of the biological membranes - especially those of the myelin sheath and platelets - as predisposing factor for the increased platelet aggregation is possible. Even though

these ideas do not yet allow a concrete pathogenetic conclusion, the prostaglandins (PG) might be of importance because their precursors are fatty acids and influence the immune mechanisms. Possibly, new approaches follow from the synopsis of present working hypotheses for an extended biochemical-immunological model of multiple sclerosis. Further immunological and laboratory methods should concentrate on differentiating MS from other diseases of the central nervous system and on diagnosing the disease in its early stage. The results of this work are fully discussed in other publications. Separate prints can be requested from the author.

Essential fatty acids in the serum and cerebrospinal fluid of multiple sclerosis patients.

Neu IS
Acta Neurol Scand (Denmark) Mar 1983, 67 (3) p151-63

Statistical evaluation of essential fatty acids (determined by gas chromatography) in the serum and cerebrospinal fluid of patients with definite MS and acute CCT showed marked differences as compared to healthy subjects. It was also evident that the decrease of essential fatty acids in MS patients differed from that of CCT patients. Whereas the fatty acid levels in the serum of MS patients revealed only minor differences as compared to the controls and CCT patients, MS patients did show a clear decrease, especially of linoleic and arachidonic acids, in the CSF. This difference was most pronounced in cholesterol esters in the CSF. One absorption study with safflower oil demonstrated normal enteral absorption of essential fatty acids and the ability to cross the blood-CSF barrier.

Multiple sclerosis: the rational basis for treatment with colchicine and evening primrose oil.

Horrobin DF
Med Hypotheses (England) Mar 1979, 5 (3) p365-78

Multiple sclerosis (MS) is a disease with no known treatment. In view of this and of its distressing nature patients are attracted by any new concepts. As a reaction to this neurologists are sometimes excessively sceptical and fail to consider new approaches seriously. Recent attempts have been made to treat multiple sclerosis with polyunsaturated fatty acids and with colchicine. This approach is not arbitrary and is firmly grounded in fundamental basic scientific concepts. In patients with multiple sclerosis there is evidence of both an abnormality in essential fatty acid metabolism and an abnormality in lymphocyte function. It is now apparent that the fatty acid abnormality may cause the lymphocyte abnormality and that both may be improved by dietary manipulation. There is also evidence that the demyelination may be associated with recurrent inflammatory episodes and with entry of calcium into the cytoplasm. In vitro colchicine has

been shown to have actions compatible with regulation of cytoplasmic calcium and in two diseases characterised by intermittent inflammatory episodes (Behcets syndrome and familial Mediterranean fever) it has been found to prevent or to reduce the severity of such episodes. Preliminary results suggest that combined therapy with evening primrose oil and colchicine may be of considerable value.

Red blood cell and adipose tissue fatty acids in mild inactive multiple sclerosis.

Nightingale S, Woo E, Smith AD, French JM, Gale MM, Sinclair HM, Bates D, Shaw DA
Department of Neurology, Royal Victoria Infirmary, Newcastle upon Tyne.
Acta Neurol Scand (Denmark) Jul 1990, 82 (1) p43-50

The fatty acid profiles of phosphatidyl ethanolamine (PE) and phosphatidyl choline (PC) of the red blood cells of 30 patients with mild inactive multiple sclerosis (MS) and 30 healthy controls were studied by gas chromatography. The groups were well matched for factors likely to influence tissue lipid levels, including diet. The MS patients showed a significant reduction in PE eicosapentaenoic acid ($p = 0.009$) especially in women, and an increase in both PE dihomo-gamma-linolenic acid ($p = 0.004$) and PC stearic acid ($p = 0.04$). No reduction in linoleic acid was observed in either the PC or PE fractions of the MS subjects. A similar study of the fatty acid profile in adipose tissue in 26 MS and 35 healthy controls found no detectable eicosapentaenoic acid in either group. However, whereas docosahexaenoic acid was not detectable in any MS patient, 40% of the controls had measurable levels varying from to 0.1 to 0.3% of total estimated fatty acid ($p = 0.0003$). No reduction in linoleic acid in MS subjects was observed. Supplementation with oral fish body oil demonstrated that n-3 fatty acids were incorporated into red blood cells over 5 weeks and this occurred equally in MS and controls. The effects of oral supplementation on adipose tissue were studied after 1 and 2 years. Whereas many fatty acids such as linoleic acid were raised at 1 year, but did not rise subsequently, eicosapentaenoic acid and docosahexaenoic acid continued to rise through the 2-year period.

Multiple sclerosis: effect of gamma linolenate administration upon membranes and the need for extended clinical trials of unsaturated fatty acids.

Field EJ, Joyce G
Eur Neurol (Switzerland) 1983, 22 (1) p78-83

Electrophoretic mobility studies of red blood cells from subjects with multiple sclerosis indicate that treatment with unsaturated fatty acids must continue for at least 2 years before normal reactivity is restored by currently available tests. If this applies to myelin also, then clinical trials aimed at treating the recognized

multiple sclerosis subject by polyunsaturated fatty acids really begin after 2 years, and this should be recognized when a trial program is drawn up.

The nutritional regulation of T lymphocyte function.

Horrobin DF, Manku MS, Oka M, Morgan RO, Cunnane SC, Ally AI, Ghayur T, Schweitzer M, Karmali RA
Med Hypotheses (England) Sep 1979, 5 (9) p969-85

Prostaglandin (PG) E1 plays a major role in the regulation of thymus development and T lymphocyte function and the evidence for this is reviewed. The production of PGE1 is dependent on nutritional factors with linoleic acid, gamma-linolenic acid, pyridoxine, zinc and Vitamin-C playing key roles. Inadequate intake of any one of these will lead to inadequate PGE1 formation and defective T lymphocyte function. Megadoses of any one are likely to be only minimally effective in the absence of adequate intakes of the others. By careful attention to diet it should be possible to activate T lymphocyte function in the large number of diseases including rheumatoid arthritis, various auto-immune diseases, multiple sclerosis, and cancer in which such function is defective. It is possible that T lymphocytes may require both endogenous and exogenous PGE1 in order to function adequately. It is therefore of particular interest that many cancer cells and virally infected cells are unable to make PGE1 because they cannot convert linoleic acid to gamma-linolenic acid. The direct provision of gamma-linolenic or dihomo-gammalinolenic acids in these situations is worthy of full investigation.

Polyunsaturated fatty acids in treatment of acute remitting multiple sclerosis.

Bates D, Fawcett PR, Shaw DA, Weightman D
Br Med J (England) Nov 18 1978, 2 (6149) p1390-1

One hundred and sixteen patients with acute remitting multiple sclerosis (MS) took part in a double-blind controlled trial of treatment with polyunsaturated fatty acids and were randomly allocated to one of four groups. Two groups received linoleic acid, one alone as a spread and one with gamma-linolenic acid in capsules (Naudicelle); and two control groups received oleic acid, one as a spread and one in capsules. Rates of clinical deterioration and frequencies of attacks were not significantly different between treated and control groups. Exacerbations were shorter and less severe in patients receiving a high dose of linoleic acid than in controls, but those receiving a lower dose--that is, Naudicelle--showed no such difference. Thus supplementing the diet with 20 g linoleic acid marginally affected the duration and severity of relapses of MS but had no effect on overall disability. The dose of Naudicelle used provided insufficient supplementation.

Effect of prolonged ingestion of gamma-linolenate by MS patients.

Field EJ, Joyce G
Eur Neurol (Switzerland) 1978, 17 (2) p67-76

The absolute electrophoretic mobility of erythrocytes from MS patients is reduced in the presence of 0.08 mg/ml of linoleic or arachidonic acid, whilst that of normal or other neurological disease patients is increased in the presence of these acids. When an MS patient ingests gamma-linolenate (in capsule form equivalent to 413.4 mg of gamma-linolenic acid and 2.664 g of linoleic acid per day) the reaction of MS erythrocytes begins to change. After 3 or 4 months the reaction becomes normal with arachidonic acid (i.e. mobility is speeded up) and 2 months or so later this occurs also with linoleic acid. Very prolonged administration of gamma-linolenate leads to a markedly increased sensitivity to the effect of prostaglandins (PGE2) on RBC mobility. The observations are interpreted to mean the induction of a biochemical-biophysical change in the membranes, and the significance of this in the aetiology and treatment of multiple sclerosis is discussed.

Experimental and clinical studies on dysregulation of magnesium metabolism and the aetiopathogenesis of multiple sclerosis.

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Division of Neurological Diseases, Wakayama Medical College, Japan.
Magnes Res (England) Dec 1992, 5 (4) p295-302

The proposed aetiologies of multiple sclerosis (MS) have included immunological mechanisms, genetic factors, virus infection and direct or indirect action of minerals and/or metals. The processes of these aetiologies have implicated magnesium. Magnesium and zinc have been shown to be decreased in central nervous system (CNS) tissues of MS patients, especially tissues such as white matter where pathological changes have been observed. The calcium content of white matter has also been found to be decreased in MS patients. The interactions of minerals and/or metals such as calcium, magnesium, aluminium and zinc have also been evaluated in CNS tissues of experimental animal models. These data suggest that these elements are regulated by pooling of minerals and/or metals in bones. Biological actions of magnesium may affect the maintenance and function of nerve cells as well as the proliferation and synthesis of lymphocytes. A magnesium deficit may induce dysfunction of nerve cells or lymphocytes directly and/or indirectly, and thus magnesium depletion may be implicated in the aetiology of MS. The action of zinc helps to prevent virus infection, and zinc deficiency in CNS tissues of MS patients may also be relevant to its aetiology. Magnesium interacts with other minerals and/or metals such as calcium, zinc and aluminium in biological systems, affecting the immune system and influencing

the content of these elements in CNS tissues. Because of these interactions, a magnesium deficit could also be a risk factor in the aetiology of MS.