

LE Magazine May 2003

## ABSTRACTS

## Testosterone

Testosterone supplementation therapy for older men: potential benefits and risks.

Serum testosterone levels decline gradually and progressively with aging in men. Many manifestations associated with aging in men, including muscle atrophy and weakness, osteoporosis, reduced sexual functioning and increased fat mass, are similar to changes associated with testosterone deficiency in young men. These similarities suggest that testosterone supplementation may prevent or reverse the effects of aging. A MEDLINE search was performed to identify studies of testosterone supplementation therapy in older men. A structured, qualitative review was performed of placebo-controlled trials that included men aged 60 and older and evaluated one or more physical, cognitive, affective, functional or quality-of-life outcomes. Studies focusing on patients with severe systemic diseases and hormone deficiencies related to specific diseases were excluded. In healthy older men with low-normal to mildly decreased testosterone levels, testosterone supplementation increased lean body mass and decreased fat mass. Upper and lower body strength, functional performance, sexual functioning and mood were improved or unchanged with testosterone replacement. Variable effects on cognitive function were reported, with improvements in some cognitive domains (e.g., spatial, working and verbal memory). Testosterone supplementation improved exercise-induced coronary ischemia in men with coronary heart disease, whereas angina pectoris was improved or unchanged. In a few studies, men with low testosterone levels were more likely to experience improvements in lumbar bone mineral density, self-perceived functional status, libido, erectile function and exercise-induced coronary ischemia with testosterone replacement than men with less marked testosterone deficiency. No major unfavorable effects on lipids were reported, but hematocrit and prostate specific antigen levels often increased. Based on these results, testosterone supplementation cannot be recommended at this time for older men with normal or low-normal testosterone levels and no clinical manifestations of hypogonadism. However, testosterone replacement may be warranted in older men with markedly decreased testosterone levels, regardless of symptoms, and in men with mildly decreased testosterone levels and symptoms or signs suggesting hypogonadism. The long-term safety and efficacy of testosterone supplementation remain uncertain. Establishment of evidence-based indications will depend on further demonstrations of favorable clinical outcomes and symptomatic, functional and quality-of-life benefits in carefully performed, long-term, randomized, placebo-controlled clinical trials.

J Am Geriatr Soc 2003 Jan;51(1):101-115

Testosterone, cytochrome P450 and cardiac hypertrophy.

Cytochrome P450 mono-oxygenases (CYP) play an essential role in steroid metabolism, and there is speculation that sex hormones might influence cardiac mass and physiology. As CYP mono-oxygenases activity is frequently altered during disease, we tested our hypothesis that CYP mono-oxygenase expression and testosterone metabolism are altered in cardiac hypertrophy. We investigate major CYP mono-oxygenase isoforms and other steroid-metabolizing enzymes and the androgen receptor in normal, hypertrophic, and assist device-supported human hearts and in spontaneously hypertensive rats (SHR). We show increased and idiosyncratic metabolism of testosterone in hypertrophic heart and link these changes to altered CYP mono-oxygenase expression. We show significant induction of 5-alpha steroid reductase and P450 aromatase gene expression and enhanced production of dihydrotestosterone, which can be inhibited by the 5-alpha reductase inhibitor finasteride. We show increased gene expression of the androgen receptor and increased levels of lipid peroxidation in diseased hearts, the latter being markedly inhibited by CYP mono-oxygenase inactivation. We show alpha-MHC to be significantly repressed in cardiac hypertrophy and restored to normal on testosterone supplementation. We conclude that heart-specific steroid metabolism is of critical importance in cardiac hypertrophy.

FASEB J 2002 Oct;16(12):1537-49

The effect of testosterone on regional blood flow in prepubertal anaesthetized pigs.

This work was undertaken to study the effects of testosterone on the coronary, mesenteric, renal and iliac circulations and to determine the mechanisms of action involved. In prepubertal pigs of both sexes anaesthetized with sodium pentobarbitone, changes in left circumflex or anterior descending coronary, superior mesenteric, left renal and left external iliac blood flow caused by intra-arterial infusion of testosterone were assessed using electromagnetic flowmeters. Changes in heart rate and arterial blood pressure were prevented by atrial pacing and by connecting the arterial system to a pressurized reservoir containing Ringer solution. In 12

pigs, intra-arterial infusion of testosterone for five minutes to achieve a stable intra-arterial concentration of 1 microg l(-1) increased coronary, mesenteric, renal and iliac blood flow without affecting the maximum rate of change of left ventricular systolic pressure (left ventricular dP/dt(max)) and filling pressures of the heart. In a further five pigs, a concentration-response curve was obtained by graded increases in the intra-arterial concentration of the hormone between 0.125 and 8 microg l(-1). The mechanisms of these responses were studied in the 12 pigs by repeating the experiment after haemodynamic variables had returned to the control values before infusions. In six pigs, blockade of muscarinic cholinergic receptors and adrenoceptors with atropine, propranolol and phentolamine did not affect the responses caused by intra-arterial infusion of testosterone performed to achieve a stable intra-arterial concentration of 1 microg l(-1). In the same pigs and in the remaining six pigs, the increases in coronary, mesenteric, renal and iliac blood flow caused by intra-arterial infusion of testosterone performed to achieve a stable intra-arterial concentration of 1 microg l(-1) were prevented by intra-arterial injection of N(omega)-nitro-L-arginine methyl ester. The present study shows that intra-arterial infusion of testosterone dilated coronary, mesenteric, renal and iliac circulations. The mechanism of this response involved the release of nitric oxide.

J Physiol 2002 Aug 15;543(Pt 1):365-72

Cyclosporine adversely affects baroreflexes via inhibition of testosterone modulation of cardiac vagal control.

Previous studies have shown that the immunosuppressant drug cyclosporine A attenuates arterial baroreceptor function. This study investigated whether the modulatory effect of cyclosporine on baroreceptor function involves inhibition of the baroreflex-facilitatory effect of testosterone. The role of cardiac autonomic control in cyclosporine-testosterone baroreflex interaction was also investigated. Baroreflex curves relating bradycardic responses to increments in blood pressure evoked by phenylephrine were constructed in conscious, sham-operated, castrated rats and in testosterone-replaced castrated (CAS + T) rats in the absence and presence of cyclosporine. The slopes of the curves were taken as an index of the baroreflex sensitivity (BRS). Short-term (11 to 13 days) cyclosporine treatment or castration reduced plasma testosterone levels and caused similar attenuation of the reflex bradycardia, as indicated by the significantly smaller BRS compared with sham-operated values (-0.97 +/- 0.07, -0.86 +/- 0.06, and -1.47 +/- 0.10 beats/min/mm Hg, respectively). The notion that androgens facilitate baroreflexes is further confirmed by the observation that testosterone replacement of castrated rats restored plasma testosterone and BRS to sham-operated levels. Cyclosporine had no effect on BRS in castrated rats but caused a significant reduction in CAS + T rats. Muscarinic blockade by atropine caused approximately 60% reduction in the BRS in sham-operated rats, an effect that was significantly and similarly diminished by castration, cyclosporine, or their combination. beta-Adrenergic blockade by propranolol caused no significant changes in BRS. These findings suggest that cyclosporine attenuates baroreflex responsiveness via, at least partly, inhibition of the testosterone-induced facilitation of cardiomotor vagal control.

J Pharmacol Exp Ther 2002 Apr;301(1):346-54

Sex hormone-binding globulin levels and cardiovascular risk factors in morbidly obese subjects before and after weight reduction induced by diet or malabsorptive surgery.

One of the main goals of weight reduction in morbidly obese subjects is its benefit on coronary heart disease (CHD) risk. A cross-sectional study was designed to randomly assign 79 morbidly obese subjects (27 men and 52 women; age: 30 to 45 years) either to a diet protocol (20 kcal per kg fat-free mass (FFM); 55% carbohydrates, 30% fat and 15% proteins) or to malabsorptive surgery (biliopancreatic diversion). Fatness parameters, measured by dual-energy X-ray absorptiometry, lipid profile, insulin, leptin, sex steroid hormones and sex hormone-binding globulin (SHBG) levels were compared at baseline and one year after the beginning of the study. The data showed that plasma SHBG levels, but not testosterone levels, correlated negatively to fasting insulin levels and positively to HDL-cholesterol in both men and women. Total leptin levels were significantly lower ( $P < 0.0001$ ) in post-BPD subjects of both sexes compared to dietary treated obese subjects. The logarithm of plasma leptin correlated significantly and positively with insulin but negatively with SHBG. A step-down regression analysis showed that FFM and SHBG, but not insulin levels, were the most powerful independent variables for predicting HDL-cholesterol levels in morbidly obese patients. The negative relationship between SHBG levels and CHD risk appears to be mediated by a concomitant variation in body fatness. Finally, in obese patients, SHBG levels seem to be an indicator of total adiposity rather than an index of an altered insulin/glucose homeostasis.

Atherosclerosis 2002 Apr;161(2):455-62

Effect of intravenous testosterone on myocardial ischemia in men with coronary artery disease.

**BACKGROUND:** Studies on the effect of estrogen on atherosclerotic coronary artery disease (CAD) risk in women have produced conflicting results. Similar confusion, but fewer data, exists on the effect of testosterone on CAD risk in men. **METHODS:** We used  $^{99m}\text{Tc}$  sestamibi single-photon emission computed tomography (SPECT) myocardial perfusion imaging to examine the acute effect of intravenous testosterone in 32 men (mean age, 69.1 +/- 6.4 years) with provokable myocardial ischemia on standard medical therapy. Patients performed three exercise ( $n = 18$ ) or adenosine ( $n = 16$ ) stress tests during the infusion of placebo or two doses of testosterone designed to increase testosterone two or six times baseline. **RESULTS:** Serum testosterone increased 137 +/- 58% and 488 +/- 113%, and estradiol levels increased 27 +/- 46% and 76 +/- 57%, ( $P < .001$  for all) during the two testosterone infusions.

There were no differences between the placebo or testosterone groups in peak heart rate, systolic blood pressure, maximal rate pressure product, perfusion imaging scores or the onset of ST-segment depression. CONCLUSIONS: Acute testosterone infusion has neither a beneficial nor a deleterious effect on the onset and magnitude of stress-induced myocardial ischemia in men with stable CAD.

Am Heart J 2002 Feb;143(2):249-56

Testosterone increases blood pressure and cardiovascular and renal pathology in spontaneously hypertensive rats.

The objective of this paper was to test the hypothesis that testosterone (T) raises blood pressure (BP), which is associated with increased coronary adventitial collagen, whereas the hemodynamic force of BP increases the coronary media:lumen ratio. Five treatment groups of spontaneously hypertensive rat (SHR) were established (n = 8-10 per group): controls; hydralazine (HYZ); castration; castration + HYZ; and castration + HYZ + T + captopril. At 12 weeks of age, the castrate + HYZ group was divided so that the mean BP was the same in both groups (162 mmHg). Both groups continued to receive HYZ treatment; however one group received T implants. Also, at 12 weeks of age the castrate + HYZ + T + captopril group received T implants. BP in the HYZ group was reduced compared with controls (192 mmHg vs 218 mmHg,  $p < 0.01$ ). Castration lowered BP to 170 mmHg ( $p < 0.01$ ) compared with controls. However, T implants increased BP by 15 mmHg ( $p < 0.02$ ) in the castrate + HYZ group and by 44 mmHg in the castrate + HYZ + captopril group ( $p < 0.01$ ). Captopril in combination with HYZ significantly reduced BP compared with controls but T replacement increased BP and coronary collagen deposition in spite of HYZ and captopril treatment.

Blood Press 2000;9(4):227-38

Effect of testosterone replacement on whole body glucose utilization and other cardiovascular risk factors in males with idiopathic hypogonadotropic hypogonadism.

**BACKGROUND:** Excessive testosterone in males or estrogens in females could explain their differences in coronary heart disease event rates. As a contraceptive testosterone is likely to be used at large scale. The role of testosterone in increasing the risks of coronary heart disease needs investigation. **AIM:** To look at the role of testosterone in development of insulin resistance and other cardiovascular risk factors. **DESIGN:** Prospective, before-after study on 10 male subjects with idiopathic hypogonadotropic hypogonadism pre- and post-testosterone replacement therapy; outcome measures: anthropometry, lipoprotein profile and M value (whole body glucose disposal rates on standard hyperinsulinemic euglycemic clamp; at insulin infusion rate:  $40 \text{ mU} \times (\text{m}^{-2})$ ). **RESULTS:** Pre-treatment serum testosterone was  $0.43 (0.515) \text{ ng} \times \text{mL}^{-1}$ , LH was  $1.29 (0.08) \text{ IU} \times \text{L}^{-1}$ , and FSH was  $1.54 (0.08) \text{ IU} \times \text{L}^{-1}$ . None had glucose intolerance. After replacement testosterone levels increased to  $9.4 \text{ ng} \times \text{mL}^{-1}$  ( $p=0.0005$ ); weight increase of  $5.0 \text{ kg}$  ( $p=0.140$ ), body mass index increase of  $1.2 \text{ kg} \times \text{m}^{-2}$  ( $p=0.28$ ), and the change in waist to hip ratio ( $p=0.31$ ) were not statistically significant. M-value ( $\text{mg} \times \text{kg} \times \text{min}^{-1}$ ) did not change after testosterone therapy ( $5.86 [0.72]$  vs  $5.29 [0.82]$ ,  $p=0.62$ ). Insulin levels ( $\text{mU} \times \text{L}^{-1}$ ) achieved during the clamps were  $89.5 (14.2)$  before and  $146 (32.2)$  after androgen therapy ( $p=0.127$ ). There was no change in glucose area under curve ( $\text{mg} \times \text{min} \times \text{dL}^{-1}$ ) ( $14406 [502.2]$  vs  $12557 [826.5]$ ,  $p=0.312$ ). On testosterone replacement therapy total and LDL cholesterol levels ( $\text{mg} \times \text{dL}^{-1}$ ) declined ( $122.5 [13.4]$  vs  $91.6 [5.0]$ ,  $p=0.04$ ;  $65.9 [9.9]$  vs  $39.4 [7.3]$ ,  $p=0.05$ ); Ratio of total cholesterol to HDL ratio also decreased significantly ( $p=0.05$ ). Changes of serum triglycerides ( $p=0.25$ ) and HDL cholesterol ( $p=0.19$ ) did not attain statistical significance. **CONCLUSIONS:** Insulin sensitivity does not decrease on testosterone replacement therapy of male subjects with idiopathic hypogonadotropic hypogonadism. Testosterone replacement was associated with decrease in other cardiovascular risk factors.

Horm Metab Res 1998 Oct;30(10):642-5

Testosterone-propionate impairs the response of the cardiac capillary bed to exercise.

**OBJECTIVE:** Experimental application of anabolic-androgenic steroids and exercise training induce cardiac hypertrophy. This study quantifies for the first time, on microscopical level, the adaptation of the cardiac capillaries and myocytes to the concomitant application of testosterone-propionate and exercise training. **METHODS:** Female SPF-NMRI mice were studied over three and six week Experimental groups: (i) sedentary control (C); (ii) exercise (treadmill running, E); (iii) testosterone-propionate (TP); and (iv) testosterone-propionate+exercise (TPE). Morphometric parameters: 1) papillary muscles: capillary density, intercapillary distance, number of capillaries around a myocyte, and minimal myocyte diameter; and 2) left ventricular wall: capillary density and intercapillary distance. **RESULTS:** Papillary muscle: A striking suppression of the exercise-induced improvement in capillary supply occurs in the testosterone-propionate+exercise groups over three and six week Exercise without drugs increases significantly ( $P < 0.05$ ) the capillary density, shortens significantly ( $P < 0.05$ ) the intercapillary distance, whereas it increases the number of capillaries around a myocyte. These alterations are not observed in the testosterone-propionate treated sedentary animals; e.g., capillary density after 6 week (mean values +/- standard deviation, capillaries  $\times \text{mm}^{-2}$ ): C:  $4272 \pm 287$ , E:  $5411 \pm 758$ , TP:  $4221 \pm 364$ , and TPE:  $3997 \pm 397$ . Moreover, only in the testosterone-propionate+exercise groups occurs a mild myocyte hypertrophy after both time periods: there is a trend toward hypertrophy ( $P < 0.1$ ) in comparison with the C groups and a significant hypertrophy ( $P < 0.05$ ) in comparison with the E groups. **CONCLUSIONS:** Testosterone-propionate profoundly inhibits the exercise-induced augmented capillarization, whereas (under training conditions) it leads to a mild myocyte hypertrophy. The microvascular

impairment could trigger an imbalance between the myocardial oxygen supply and demand, especially during physical exercise.

Med Sci Sports Exerc 2000 May;32(5):946-53

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## ABSTRACTS

Effects of testosterone on coronary vasomotor regulation in men with coronary heart disease.

**BACKGROUND:** The increased incidence of coronary artery disease in men compared with premenopausal women suggests a detrimental role of male hormones on the cardiovascular system. However, testosterone has direct relaxing effects on coronary arteries in animals, as shown both in vitro and in vivo. The effect of testosterone on the human coronary circulation remains unknown. **METHODS AND RESULTS:** We studied 13 men (aged 61±11 years) with coronary artery disease. They underwent measurement of coronary artery diameter and blood flow after a three-minute intracoronary infusion of vehicle control (ethanol) followed by two-minute intracoronary infusions of acetylcholine (10<sup>-7</sup> to 10<sup>-5</sup> mol/L) until peak velocity response. A dose-response curve to three-minute infusions of testosterone (10<sup>-10</sup> to 10<sup>-7</sup> mol/L) was then determined, and the acetylcholine infusions were repeated. Finally, an intracoronary bolus of isosorbide dinitrate (1000 microgram) was given. Coronary blood flow was calculated from measurements of blood flow velocity using intracoronary Doppler and coronary artery diameter using quantitative coronary angiography. Testosterone significantly increased coronary artery diameter compared with baseline (2.78±0.74 mm versus 2.86±0.72 mm [P=0.05], 2.87±0.71 mm [P=0.038], and 2.90±0.75 mm [P=0.005] for baseline versus testosterone 10<sup>-9</sup> to 10<sup>-7</sup> mol/L, respectively). A significant increase in coronary blood flow occurred at all concentrations of testosterone compared with baseline (geometric mean [95% CI]: 32 [25, 42] versus 36.3 [27, 48] inverted question markP=0.006 inverted question mark, 35.3 [26, 47] inverted question markP=0.029 inverted question mark, 36.8 [28, 49] inverted question markP=0.002 inverted question mark, and 37 [28, 48] inverted question markP=0.002 inverted question mark mL/min for baseline versus testosterone 10<sup>-10</sup> to 10<sup>-7</sup> mol/L, respectively). No differences existed in coronary diameter or blood flow responses to acetylcholine before versus after testosterone. **CONCLUSIONS:** Short-term intracoronary administration of testosterone, at physiological concentrations, induces coronary artery dilatation and increases coronary blood flow in men with established coronary artery disease.

Circulation 1999 Oct 19;100(16):1690-6

Testosterone and other anabolic steroids as cardiovascular drugs.

There has been much interest in the effect of sex hormones on cardiovascular risk factors and as a therapeutic modality in both men and women. In this article, testosterone is considered as a possible therapy for cardiovascular disease. It has been shown that the level of serum testosterone decreases in men as they age. Healthy men with low testosterone levels have increased cardiovascular risk factors, including high fasting and two-hour plasma glucose, serum triglycerides, total cholesterol and low-density lipoprotein (LDL) cholesterol, and apo A-I lipoprotein. Injections of testosterone to raise the levels to midnormal range have been shown to decrease total cholesterol and LDL cholesterol, while increasing high-density lipoprotein (HDL) cholesterol. Testosterone affects the clotting system by increasing thromboxane A<sub>2</sub> receptor activity and platelet aggregability. Testosterone has also been shown to augment the fibrinolytic system and antithrombin III activity. In men, testosterone has been shown to have antianginal effects, and endogenous levels have an inverse relationship to systolic blood pressure. Testosterone can be given in oral, injectable, pellet and transdermal patch forms. There may be a role in administering testosterone to return men to normal physiologic range who have low serum levels. This treatment increases the risk of prostatic cancer, benign prostatic hyperplasia, erythrocytosis and edema. No long-term studies of the effects of long-term testosterone replacement have been undertaken, so it is difficult to recommend this treatment as yet, but it is being considered as a therapy for augmenting skeletal muscle strength in patients with congestive heart failure.

Am J Ther 1999 May;6(3):167-74

The association of low plasma testosterone level with coronary artery disease in Chinese men.

The incidence rate and mortality of coronary heart disease (CHD) is obviously higher in men than in women, which may be related to the influence of plasma lipoprotein metabolism by endogenous sex hormones. We determined plasma testosterone (TTT), estradiol, total cholesterol (TC), triglyceride (TG), high density lipoprotein-cholesterol (HDL-C), HDL<sub>2</sub>-C, HDL<sub>3</sub>-C, apolipoprotein (Apo) AI, Apo B100 and lipoprotein (a) [Lp(a)] in 201 subjects, among them 102 patients with CHD and 99 healthy subjects. It was found that, mean plasma TTT levels in patients with CAD (252±125 ng/ml) was significantly lower than in the healthy subjects (412±309 ng/ml). There was a negative association between plasma TTT level and plasma TG level (r=-0.239; P<0.001) and Lp(a) (r=-0.163, P<0.05), and a positive association between plasma TTT level and HDL-C (r=0.301, P<0.001) and HDL<sub>3</sub>-C (r=0.328, P<0.001). The results in the present study suggest that low plasma TTT level may be a risk factor for CHD, which may relate to the influence of plasma lipoprotein metabolism by endogenous testosterone.

Int J Cardiol 1998 Jan 31;63(2):161-4

Decreased serum testosterone in men with acute ischemic stroke.

Serum levels of total and free testosterone and 17 beta-estradiol were determined in 144 men with acute ischemic stroke and 47 healthy male control subjects. Blood samples from patients were drawn a mean of three days after stroke onset and also six months after admission in a subgroup of 45 patients. Initial stroke severity was assessed on the Scandinavian Stroke Scale and infarct size by computed tomographic scan. Mean total serum testosterone was 13.8 +/- 0.5 nmol/L in stroke patients and 16.5 +/- 0.7 nmol/L in control subjects ( $P = .002$ ); the respective values for free serum testosterone were 40.8 +/- 1.3 and 51.0 +/- 2.2 pmol/L ( $P = .0001$ ). Both total and free testosterone were significantly inversely associated with stroke severity and six-month mortality, and total testosterone was significantly inversely associated with infarct size. The differences in total and free testosterone levels between patients and control subjects could not be explained by 10 putative risk factors for stroke, including age, blood pressure, diabetes, ischemic heart disease, smoking and atrial fibrillation. Total and free testosterone levels tended to normalize six months after the stroke. There was no difference between patients and control subjects in serum 17 beta-estradiol levels. These results support the idea that testosterone affects the pathogenesis of ischemic stroke in men.

Arterioscler Thromb Vasc Biol 1996 Jun;16(6):749-54

SAMe

S-adenosylmethionine improves depression in patients with Parkinson's disease in an open-label clinical trial.

We report a pilot study of S-adenosylmethionine (SAMe) in 13 depressed patients with Parkinson's disease. All patients had been previously treated with other antidepressant agents and had no significant benefit or had intolerable side effects. SAMe was administered in doses of 800 to 3600 mg per day for a period of 10 weeks. Eleven patients completed the study, and 10 had at least a 50% improvement on the 17-point Hamilton Depression Scale (HDS). One patient did not improve. Two patients prematurely terminated participation in the study because of increased anxiety. One patient experienced mild nausea, and another two patients developed mild diarrhea, which resolved spontaneously. The mean HDS score before treatment was 27.09 +/- 6.04 (mean +/- standard deviation) and was 9.55 +/- 7.29 after SAMe treatment ( $p < 0.0001$ ). Although uncontrolled and preliminary, this study suggests that SAMe is well tolerated and may be a safe and effective alternative to the antidepressant agents currently used in patients with Parkinson's disease.

Mov Disord 2000 Nov;15(6):1225-9

Rapidity of onset of the antidepressant effect of parenteral S-adenosylmethionine.

A possible method of reducing the delay in antidepressant response is to use S-adenosylmethionine (SAMe), a naturally occurring compound that appears to have a rapid onset of effect in the treatment of depression. In this open, multicenter study, 195 patients were given 400 mg of SAMe, administered parenterally, for 15 days. Depressive symptoms remitted after seven and 15 days of treatment with SAMe, and no serious adverse events were reported. Further studies with a double-blind design are needed to confirm this preliminary indication that SAMe is a relatively safe and fast-acting antidepressant.

Psychiatry Res 1995 Apr 28;56(3):295-7

Role of S-adenosylmethionine in the treatment of depression: a review of the evidence.

Major depression remains difficult to treat, despite the wide array of registered antidepressants available. In recent years there has been a surge in the popularity of natural or alternative medications. Despite this growing popularity, there is limited evidence for the effectiveness of many of these natural treatments. S-adenosylmethionine (SAMe) is one of the better studied of the natural remedies. SAMe is a methyl donor and is involved in the synthesis of various neurotransmitters in the brain. Derived from the amino acid L-methionine through a metabolic pathway called the one-carbon cycle, SAMe has been postulated to have antidepressant properties. A small number of clinical trials with parenteral or oral SAMe have shown that, at doses of 200 to 1600 mg/d, SAMe is superior to placebo and is as effective as tricyclic antidepressants in alleviating depression, although some individuals may require higher doses. SAMe may have a faster onset of action than do conventional antidepressants and may potentiate the effect of tricyclic antidepressants. SAMe may also protect against the deleterious effects of Alzheimer's disease. SAMe is well tolerated and relatively free of adverse effects, although some cases of mania have been reported in bipolar patients. Overall, SAMe appears to be safe and effective in the treatment of depression, but more research is needed to determine optimal doses. Head-to-head comparisons with newer antidepressants should help to clarify SAMe's place in the psychopharmacologic armamentarium.

Am J Clin Nutr 2002 Nov;76(5):1158S-61S

Open trial of S-adenosylmethionine for treatment of depression.

Nine depressed inpatients completed trials with S-adenosylmethionine. Seven showed improvement or remission of their symptoms. As in European studies, no side effects were seen except the apparent induction of mania in two patients with bipolar disorder.

Am J Psychiatry 1984 Mar;141(3):448-50

The antidepressant potential of oral S-adenosylmethionine.

S-adenosylmethionine (SAME), a naturally occurring brain metabolite, has previously been found to be effective and tolerated well in parenteral form as a treatment of major depression. To explore the antidepressant potential of oral SAME, we conducted an open trial in 20 outpatients with major depression, including those with (n = 9) and without (n = 11) prior history of antidepressant nonresponse. The group as a whole significantly improved with oral SAME: seven of 11 non-treatment-resistant and two of nine treatment-resistant patients experienced full antidepressant response. Side effects were mild and transient.

Acta Psychiatr Scand 1990 May;81(5):432-6

The influence of S-adenosylmethionine (SAME) on prolactin in depressed patients.

Twenty subjects entered a double-blind placebo-controlled trial of SAME in depression. Prolactin concentrations were measured before and after 14 days treatment. There was a highly significant fall in prolactin concentrations in the SAME-treated group.

Int Clin Psychopharmacol 1987 Apr;2(2):97-102

S-adenosylmethionine in the treatment of Alzheimer's disease.

Patients with Alzheimer's disease (AD) have an apparent abnormality possibly representing an increase in the average fluidity of their cell membranes. Changes in membrane fluidity of similar magnitude to those observed in AD have been noted to lead to marked alterations in cell function. Therefore, the changes in fluidity observed in AD may be related to the symptoms of that disorder, representing either an underlying cause of dysfunction or cellular attempts to compensate for dysfunction in AD. To test these possibilities, we administered S-adenosylmethionine (SAME), an agent shown to increase membrane fluidity in animals, to patients with AD. Treatment with SAME led to marked increases in membrane fluidity. However, it produced neither improvement nor worsening of symptoms. The results imply that while SAME may be useful for other conditions associated with altered membrane fluidity (such as normal aging), changing membrane fluidity per se is not likely to lead to marked changes in symptoms in AD.

J Clin Psychopharmacol 1988 Feb;8(1):43-7

C-reactive protein

Risk of cardiovascular disease in relation to achieved office and ambulatory blood pressure control in treated hypertensive subjects.

Objective: We investigated the prognostic impact of 24-hour blood pressure control in treated hypertensive subjects. Background: There is growing evidence that ambulatory blood pressure improves risk stratification in untreated subjects with essential hypertension. Surprisingly, little is known on the prognostic value of this procedure in treated subjects. Methods: Diagnostic procedures including 24-hour noninvasive ambulatory blood pressure monitoring were undertaken in 790 subjects with essential hypertension (mean age 48 years) before therapy and after an average follow-up of 3.7 years (2,891 patient-years). Results: At the follow-up visit, 26.6% of subjects achieved adequate office blood pressure control (<140/90 mm Hg), and 37.3% of subjects achieved adequate ambulatory blood pressure control (daytime blood pressure <135/85 mm Hg). Months or years after the follow-up visit, 58 patients suffered a first cardiovascular event. Event rate was lower (0.71 events/100 person-years) among the subjects with adequate ambulatory blood pressure control than among those with higher blood pressure levels (1.87 events/100 person-years) (p = 0.0026). Ambulatory blood pressure control predicted a lesser risk for subsequent cardiovascular disease independently of other individual risk factors (RR 0.36; 95% confidence intervals: 0.18 to 0.70; P = 0.003), including age, diabetes and left ventricular hypertrophy. Office blood pressure control was associated with a nonsignificant lesser risk of subsequent events (RR 0.63; 95% confidence intervals: 0.31 to 1.31; P = NS). In-treatment ambulatory blood pressure was more potent than pre-treatment blood pressure for prediction of subsequent cardiovascular disease. Conclusions: Ambulatory blood pressure control is superior to office blood pressure control for prediction of individual cardiovascular risk in treated hypertensive subjects.

J Clin Psychopharmacol 1988 Feb;8(1):43-7

C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus.

CONTEXT: Inflammation is hypothesized to play a role in development of type 2 diabetes mellitus (DM); however, clinical data

addressing this issue are limited. OBJECTIVE: To determine whether elevated levels of the inflammatory markers interleukin 6 (IL-6) and C-reactive protein (CRP) are associated with development of type 2 DM in healthy middle-aged women. DESIGN: Prospective, nested case-control study. SETTING: The Women's Health Study, an ongoing U.S. primary prevention, randomized clinical trial initiated in 1992. PARTICIPANTS: From a nationwide cohort of 27,628 women free of diagnosed DM, cardiovascular disease, and cancer at baseline, 188 women who developed diagnosed DM over a four-year follow-up period were defined as cases and matched by age and fasting status with 362 disease-free controls. MAIN OUTCOME MEASURES: Incidence of confirmed clinically diagnosed type 2 DM by baseline levels of IL-6 and CRP. RESULTS: Baseline levels of IL-6 ( $P < .001$ ) and CRP ( $P < .001$ ) were significantly higher among cases than among controls. The relative risks of future DM for women in the highest vs lowest quartile of these inflammatory markers were 7.5 for IL-6 (95% confidence interval [CI], 3.7-15.4) and 15.7 for CRP (95% CI, 6.5-37.9). Positive associations persisted after adjustment for body mass index, family history of diabetes, smoking, exercise, use of alcohol and hormone replacement therapy; multivariate relative risks for the highest vs lowest quartiles were 2.3 for IL-6 (95% CI, 0.9-5.6;  $P$  for trend = .07) and 4.2 for CRP (95% CI, 1.5-12.0;  $P$  for trend = .001). Similar results were observed in analyses limited to women with a baseline hemoglobin A(1c) of 6.0% or less and after adjustment for fasting insulin level. CONCLUSIONS: Elevated levels of CRP and IL-6 predict the development of type 2 DM. These data support a possible role for inflammation in diabetogenesis.

JAMA 2001 Jul 18;286(3):327-34

Associations of elevated interleukin-6 and C-reactive protein levels with mortality in the elderly.

PURPOSE: To investigate whether interleukin-6 and C-reactive protein levels predict all-cause and cause-specific mortality in a population-based sample of nondisabled older people. SUBJECTS AND METHODS: A sample of 1,293 healthy, nondisabled participants in the Iowa 65+ Rural Health Study was followed prospectively for a mean of 4.6 years. Plasma interleukin-6 and C-reactive protein levels were measured in specimens obtained from 1987 to 1989. RESULTS: Higher interleukin-6 levels were associated with a two-fold greater risk of death [relative risk (RR) for the highest quartile ( $> \text{or} = 3.19 \text{ pg/mL}$ ) compared with the lowest quartile of 1.9 [95% confidence interval, CI, 1.2 to 3.1]]. Higher C-reactive protein levels ( $> \text{or} = 2.78 \text{ mg/L}$ ) were also associated with increased risk (RR = 1.6; CI, 1.0 to 2.6). Subjects with elevation of both interleukin-6 and C-reactive protein levels were 2.6 times more likely (CI, 1.6 to 4.3) to die during follow-up than those with low levels of both measurements. Similar results were found for cardiovascular and noncardiovascular causes of death, as well as when subjects were stratified by sex, smoking status, and prior cardiovascular disease, and for both early ( $< 2.3$  years) and later follow-up. Results were independent of age, sex, body mass index and history of smoking, diabetes and cardiovascular disease, as well as known indicators of inflammation including fibrinogen and albumin levels and white blood cell count. CONCLUSIONS: Higher circulating levels of interleukin-6 and C-reactive protein were associated with mortality in this population-based sample of healthy older persons. These measures may be useful for identification of high-risk subgroups for anti-inflammatory interventions.

Am J Med 1999 May;106(5):506-12

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## ABSTRACTS

Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities: results from the Cardiovascular Health Study.

**BACKGROUND:** The biological basis of frailty has been difficult to establish owing to the lack of a standard definition, its complexity and its frequent coexistence with illness. **OBJECTIVE:** To establish the biological correlates of frailty in the presence and absence of concurrent cardiovascular disease and diabetes mellitus. **METHODS:** Participants were 4,735 community-dwelling adults 65 years and older. Frail, intermediate and nonfrail subjects were identified by a validated screening tool and exclusion criteria. Bivariate relationships between frailty level and physiological measures were evaluated by Pearson chi2 tests for categorical variables and analysis of variance F tests for continuous variables. Multinomial logistic regression was performed to evaluate multivariable relationships between frailty status and physiological measures. **RESULTS:** Of 4,735 Cardiovascular Health Study participants, 299 (6.3%) were identified as frail, 2,147 (45.3%) as intermediate, and 2,289 (48.3%) as not frail. Frail vs nonfrail participants had increased mean +/- SD levels of C-reactive protein (5.5 +/- 9.8 vs 2.7 +/- 4.0 mg/L), factor VIII (13,790 +/- 4,480 vs 11,860 +/- 3,460 mg/dL), and, in a smaller subset, D dimer (647 +/- 1,033 vs 224 +/- 258 ng/mL) ( $P < \text{or} = .001$  for all, chi2 test for trend). These differences persisted when individuals with cardiovascular disease and diabetes were excluded and after adjustment for age, sex and race. **CONCLUSIONS:** These findings support the hypothesis that there is a specific physiological basis to the geriatric syndrome of frailty that is characterized in part by increased inflammation and elevated markers of blood clotting and that these physiological differences persist when those with diabetes and cardiovascular disease are excluded.

Arch Intern Med 2002 Nov 11;162(20):2333-41

Inflammatory mediators are induced by dietary glycotoxins, a major risk factor for diabetic angiopathy.

Diet is a major environmental source of proinflammatory AGEs (heat-generated advanced glycation end products); its impact in humans remains unclear. We explored the effects of two equivalent diets, one regular (high AGE, H-AGE) and the other with five-fold lower AGE (L-AGE) content on inflammatory mediators of 24 diabetic subjects: 11 in a two-week crossover and 13 in a six-week study. After two weeks on H-AGE, serum AGEs increased by 64.5% ( $P = 0.02$ ) and on L-AGE decreased by 30% ( $P = 0.02$ ). The mononuclear cell tumor necrosis factor- $\alpha$ -actin mRNA ratio was 1.4 +/- 0.5 on H-AGE and 0.9 +/- 0.5 on L-AGE ( $P = 0.05$ ), whereas serum vascular adhesion molecule-1 was 1,108 +/- 429 and 698 +/- 347 ng/ml ( $P = 0.01$ ) on L- and H-AGE, respectively. After 6 weeks, peripheral blood mononuclear cell tumor necrosis factor- $\alpha$  rose by 86.3% ( $P = 0.006$ ) and declined by 20% ( $P$ , not significant) on H- or L-AGE diet, respectively; C-reactive protein increased by 35% on H-AGE and decreased by 20% on L-AGE ( $P = 0.014$ ), and vascular adhesion molecule-1 declined by 20% on L-AGE ( $P < 0.01$ ) and increased by 4% on H-AGE. Serum AGEs were increased by 28.2% on H-AGE ( $P = 0.06$ ) and reduced by 40% on L-AGE ( $P = 0.02$ ), whereas AGE low density lipoprotein was increased by 32% on H-AGE and reduced by 33% on L-AGE diet ( $P < 0.05$ ). Thus in diabetes, environmental (dietary) AGEs promote inflammatory mediators, leading to tissue injury. Restriction of dietary AGEs suppresses these effects.

Proc Natl Acad Sci U S A 2002 Nov 26;99(24):15596-601

Serum levels of the antiinflammatory cytokine interleukin-10 are decreased in patients with unstable angina.

**BACKGROUND:** Proinflammatory cytokines play a role in acute coronary events. However, the potential role of antiinflammatory cytokines in the modulation of the atherosclerotic process remains unknown. Interleukin (IL)-10, which is expressed in human atherosclerotic plaques, has potent deactivating properties in macrophages and T cells. The aim of this study was to assess whether serum concentrations of IL-10 differed between patients with unstable and stable angina pectoris. **METHODS AND RESULTS:** A total of 95 patients with angina pectoris and angiographically documented coronary artery disease were studied. Of these, 50 patients had chronic stable angina (with stable symptoms over three months), and 45 patients had Braunwald class IIIB unstable angina with ST-segment changes. Serum IL-10 and IL-6 concentrations were measured on admission using commercially available immunoassays. Serum IL-10 concentrations were lower in unstable angina patients compared with those who had chronic stable angina (28.4 versus 14.0 pg/mL; 95% CI, 9.8 to 19.0;  $P < 0.0001$ ), even after adjustment for variables that were significantly different on univariate analysis. IL-6 concentrations were higher in the unstable angina group (20.9 versus 11.4 pg/mL; 95% CI, 1.0 to 12.6;  $P = 0.04$ ). **CONCLUSIONS:** Patients with unstable angina had significantly lower serum IL-10 concentrations than did patients with chronic stable angina. This important finding is in keeping with previous data from animal model studies that suggest that IL-10 has a protective role in atherosclerosis.

Circulation 2001 Aug 14;104(7):746-9

CXC chemokine receptors expression during chronic relapsing experimental autoimmune encephalomyelitis.

Chemokines are small proinflammatory cytokines that possess the ability to stimulate migration of inflammatory cells towards the tissue site of inflammation. Previous reports showed that several chemokines may be involved in the pathogenesis of experimental autoimmune encephalomyelitis (EAE), an animal model of autoimmune central nervous system (CNS) inflammation. Inflammatory cells respond to chemotactic chemokine gradient through the chemokine receptors (ChRs). The goal of this study was to analyze expression of ChRs belonging to CXC subfamily during different stages of chronic relapsing EAE. We found significantly increased expression of CXCR2 and CXCR4 in the spinal cord during the first and second disease attacks. The kinetics of this expression in CNS and blood suggests that CXCR2 is expressed by leukocytes migrating from the blood, but CXCR4 is expressed mainly by CNS parenchymal cells. Those results support the interpretation that chemokine-chemokine receptor interactions may play an important role in the development of CNS autoimmune inflammation.

Ann N Y Acad Sci 2000;917:135-44

C-reactive protein (CRP) in the cardiovascular system.

CRP (C-reactive protein) is an acute-phase reactant, the levels of which increase dramatically in response to severe bacterial infection, physical trauma and other inflammatory conditions. CRP is found in human atherosclerotic lesions. Atherosclerosis is clearly multifactorial in origin, and chronic inflammation is an important component in its pathogenesis. Focus on inflammation is critical in research on atherosclerosis. Elevated levels of CRP have been associated with increased risk of future coronary artery disease (CAD) events. I have summarized the recent literature on CRP studies in CAD. Both coronary heart disease and dilated cardiomyopathy (DCM) result in congestive heart failure due to myocardial damage. The inflammatory state produced by myocarditis of viral or other origin may induce advanced myocardial damage, resulting in heart failure with a poor prognosis. Routine CRP measurement proved to be valuable for identifying high-risk patients with DCM and lymphocytic myocarditis. I suggest that measurement of circulating CRP would be useful for the diagnosis of and for selecting therapeutic strategies for cardiovascular disorders.

Rinsho Byori 2001 Apr;49(4):395-401

Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities: results from the Cardiovascular Health Study.

**BACKGROUND:** The biological basis of frailty has been difficult to establish owing to the lack of a standard definition, its complexity, and its frequent coexistence with illness. **OBJECTIVE:** To establish the biological correlates of frailty in the presence and absence of concurrent cardiovascular disease and diabetes mellitus. **METHODS:** Participants were 4,735 community-dwelling adults 65 years and older. Frail, intermediate, and nonfrail subjects were identified by a validated screening tool and exclusion criteria. Bivariate relationships between frailty level and physiological measures were evaluated by Pearson chi2 tests for categorical variables and analysis of variance F tests for continuous variables. Multinomial logistic regression was performed to evaluate multivariable relationships between frailty status and physiological measures. **RESULTS:** Of 4,735 Cardiovascular Health Study participants, 299 (6.3%) were identified as frail, 2,147 (45.3%) as intermediate, and 2,289 (48.3%) as not frail. Frail vs nonfrail participants had increased mean +/- SD levels of C-reactive protein (5.5 +/- 9.8 vs 2.7 +/- 4.0 mg/L), factor VIII (13,790 +/- 4,480 vs 11 860 +/- 3,460 mg/dL), and, in a smaller subset, D dimer (647 +/- 1,033 vs 224 +/- 258 ng/mL) ( $P < .001$  for all, chi2 test for trend). These differences persisted when individuals with cardiovascular disease and diabetes were excluded and after adjustment for age, sex and race. **CONCLUSIONS:** These findings support the hypothesis that there is a specific physiological basis to the geriatric syndrome of frailty that is characterized in part by increased inflammation and elevated markers of blood clotting and that these physiological differences persist when those with diabetes and cardiovascular disease are excluded.

Arch Intern Med 2002 Nov 11;162(20):2333-41

Pet health

Effect of N-acetylcysteine on gentamicin-mediated nephropathy in rats.

Studies were performed on the mechanisms of the protective effects of free-radical scavengers against gentamicin-mediated nephropathy. Administration of gentamicin, 100 mg/kg s.c., for five days to rats induced marked renal failure, characterized by a significantly decreased creatinine clearance and increased blood creatinine levels, fractional excretion of sodium Na(+), lithium Li (+), urine gamma glutamyl transferase and daily urine volume. A significant increase in kidney myeloperoxidase activity and lipid peroxidation was observed in gentamicin-treated rats. Immunohistochemical localization demonstrated nitrotyrosine formation and poly(ADP-ribose)synthase activation in the proximal tubule from gentamicin-treated rats. Renal histology examination confirmed the tubular necrosis. N-acetylcysteine (10 mg/kg i.p. for five days) caused normalization of the above biochemical parameters. In addition, N-acetylcysteine treatment significantly prevents the gentamicin-induced tubular necrosis. These results suggest that (1) N-acetylcysteine has protective effects on gentamicin-mediated nephropathy and (2) the mechanisms of the protective effects can

be, at least in part, related to interference with peroxynitrite-related pathways.

Eur J Pharmacol 2001 Jul 13;424(1):75-83

Oxidative damage increases with age in a canine model of human brain aging.

We assayed levels of lipid peroxidation, protein carbonyl formation, glutamine synthetase (GS) activity and oxidized and reduced glutathione to study the link between oxidative damage, aging and beta-amyloid (Abeta) in the canine brain. The aged canine brain, a model of human brain aging, naturally develops extensive diffuse deposits of human-type Abeta. Abeta was measured in immunostained prefrontal cortex from 19 beagle dogs (4 to 15 years). Increased malondialdehyde (MDA), which indicates increased lipid peroxidation, was observed in the prefrontal cortex and serum but not in cerebrospinal fluid (CSF). Oxidative damage to proteins (carbonyl formation) also increased in brain. An age-dependent decline in GS activity, an enzyme vulnerable to oxidative damage, and in the level of glutathione (GSH) was observed in the prefrontal cortex. MDA level in serum correlated with MDA accumulation in the prefrontal cortex. Although 11/19 animals exhibited Abeta, the extent of deposition did not correlate with any of the oxidative damage measures, suggesting that each form of neuropathology accumulates in parallel with age. This evidence of widespread oxidative damage and Abeta deposition is further justification for using the canine model for studying human brain aging and neurodegenerative diseases.

J Neurochem 2002 Jul;82(2):375-81

Oxidative stress participates in the breakdown of neuronal phenotype in experimental diabetic neuropathy.

AIMS/HYPOTHESIS: This study compared the effects of streptozotocin-induced diabetes in rats with those of two pro-oxidant interventions; a diet deficient in vitamin E and treatment with primaquine. METHODS: Measurements were made by the classic motor and sensory conduction velocity deficits and by indicators of the breakdown of small fibre phenotype i.e., sciatic nerve content of nerve growth factor and the neuropeptides, substance P and neuropeptide Y. RESULTS: As with diabetes, the pro-oxidant interventions decreased conduction velocities (though the effect of vitamin E deficiency was not significant), the sciatic nerve content of nerve growth factor and the neuropeptides (all percentages refer to the mean value for the appropriate control groups). In diabetes, nerve growth factor was depleted to 50% in the control rats ( $p < 0.05$ ); oxidative stress depleted nerve growth factor to 64% (primaquine;  $p < 0.05$ ) and 81% (vitamin E deficient; not significant) of controls. Substance P was depleted to 51% in the control rats ( $p < 0.01$ ) with depletions to 74% and 72% (both  $p < 0.01$ ) by oxidative stress; equivalent depletions for neuropeptide Y were 38% controls in diabetes ( $p < 0.001$ ) and 67% (primaquine;  $p < 0.001$ ) and 74% (vitamin E deficient;  $p < 0.05$ ) for oxidative stress. CONCLUSION/INTERPRETATION: The relative magnitudes of these changes suggest an effect in diabetes of oxidative stress, coupled with some other cellular event(s). This is supported by the effects of a diester of gamma-linolenic acid and alpha-lipoic acid, which completely prevented the effects on the pro-oxidant interventions on conduction velocity, nerve growth factor and neuropeptide contents, but was only partially preventative in diabetes.

Diabetologia 2001 Apr;44(4):424-8

Assessment of dietary therapies in a canine model of Batten disease.

The neuronal ceroid lipofuscinoses (NCLs) are inherited neurodegenerative diseases that occur in a number of animal species, including dogs. A study was conducted to determine whether the resupply of nutrients lost in NCL English Setter dogs would modify the course of the disease. Carnitine and polyunsaturated fatty acids have been reported to be reduced in NCL English Setters. Therefore, the normal laboratory diets of NCL dogs were supplemented with carnitine, fish oil and corn oil and the disease progression was compared with that of an untreated litter mate. The following specific prognostic indicators of NCL were monitored: cognitive function, brain atrophy, brain glucose metabolism and lifespan. Carnitine, with or without lipid supplements, dramatically delayed the progression of cognitive decline in NCL dogs. When fish oil and corn oil only were supplied, brain atrophy was reduced. A combination of all three supplements preserved cognitive function and increased lifespan by 10%. However, brain glucose hypometabolism and cerebral atrophy were not reduced. The results in this study indicated that the effectiveness of therapeutic interventions can be assessed by non-invasive methods at a relatively early stage of the disease process. Our study suggests that dietary supplementation with carnitine is a promising new approach for delaying or preventing the cognitive decline in dogs, and perhaps, with human NCL patients.

Eur J Paediatr Neurol 2001;5 Suppl A:151-6

Dermatosis associated with feeding generic dog food: 13 cases (1981 to 1982).

The records of 13 dogs with a crusting dermatosis of the mucocutaneous junctions, pressure points and trunk were evaluated. All of the dogs had been fed corn- and wheat-based commercial dry dog foods that failed to meet the National Research Council's recommendations for balanced nutrition. The dermatosis in all 13 dogs resolved completely after the diet was changed to one that met the National Research Council's recommendations. The disease was similar to that which has previously been called canine

dry pyoderma, but is now known to be a zinc-responsive dermatosis.

J Am Vet Med Assoc 1988 Mar 1;192(5):676-80

Dietary beta-carotene absorption by blood plasma and leukocytes in domestic cats.

Three experiments were conducted to study the uptake of oral beta-carotene by blood plasma and leukocytes in domestic cats. In Experiment 1, mature female Tabby cats (12 month old) were given once orally 0, 10, 20 or 50 mg of beta-carotene and blood taken at 0, 12, 24, 30, 36, 42, 48 and 72 hour after dosing. Concentrations of plasma beta-carotene increased in a dose-dependent manner. Peak concentrations were observed at 12-24 hour and declined gradually thereafter. The half-life of plasma beta-carotene was 12-30 hour. In Experiment 2, cats were dosed daily for six consecutive days with 0, 1, 2, 5 or 10 mg beta-carotene. Blood was sampled once daily at 12 hour after each feeding. Daily dosing of cats with beta-carotene for six days resulted in a dose-dependent increase in circulating beta-carotene. Experiment 3 was designed to study the uptake of beta-carotene by blood leukocytes. Cats were fed 0, 5 or 10 mg of beta-carotene daily for 14 days. Blood leukocytes were obtained on day seven and 14 to determine beta-carotene content in whole lymphocytes and in subcellular fractions. Blood lymphocytes took up large amounts of beta-carotene by day seven of feeding. Furthermore, beta-carotene accumulated mainly in the mitochondria (40% to 52%), with lower amounts accumulating in the microsomes (20 to 35%), cytosol (15% to 34%), and nuclei (1.5% to 6%). Therefore, domestic cats readily absorb beta-carotene across the intestinal mucosa and transfer the beta-carotene into peripheral blood leukocytes and their subcellular organelles. Beta-carotene uptake kinetics show that some aspects of beta-carotene absorption and metabolism in cats are similar to those of humans.

J Nutr 2000 Sep;130(9):2322-5

Evaluation of the components of a commercial probiotic in gnotobiotic mice experimentally challenged with *Salmonella enterica* subsp. *enterica* ser. Typhimurium.

Vitacanis((R)), a probiotic preparation containing a *Lactobacillus acidophilus*, an *Enterococcus faecium* and a *Saccharomyces cerevisiae*, has been developed for the prevention of intestinal disorders in dogs and cats. In the present study, these microorganisms were tested jointly or singly during experimental infection of gnotobiotic mice with *Salmonella typhimurium*. Four experimental groups consisting of animals given probiotics jointly or singly and a control group consisting of germfree mice were used. The groups were treated with one or three of the microorganisms (experimental) or PBS (control) 10 days before intragastric challenge with a suspension containing about  $10^{12}$  cells of the bacterial pathogen. A higher survival ( $P < 0.05$ ) was observed in gnotobiotic mice given *E. faecium* (82%). All the animals in the other groups died after the challenge but the survival time was longer ( $P < 0.05$ ) for groups given all three of the microorganisms ( $7.4 \pm 2.4$  days) or given only *L. acidophilus* ( $7.2 \pm 2.9$  days) than for the control mice ( $4.4 \pm 1.1$  days) and the mice that received *S. cerevisiae* ( $4.9 \pm 1.6$  days) mice. The survival data agreed with the histopathological findings which showed more severe liver and intestinal lesions in control mice and in mice given *Saccharomyces*. In vitro antagonistic assays showed inhibition growth of *E. faecium* and *S. Typhimurium* around the colonies of *L. acidophilus* and for *S. Typhimurium* around the colonies of *E. faecium*. However, in vivo, *S. Typhimurium* became similarly established in the digestive tract of gnotobiotic mice at levels ranging from  $10^8$  to  $10^{10}$  CFU/g of feces and remained at these high levels until the animals died or were sacrificed. Among the three probiotic components of the commercial product Vitacanis((R)), *E. faecium* was the only one that provided protection against challenge with *S. Typhimurium*. Protection was not due to the reduction of the intestinal populations of the pathogenic bacteria.

Vet Microbiol 2001 Mar 20;79(2):183-9

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