

ABSTRACTS

Inflammation

C-reactive protein, interleukin-6, and fibrinogen as predictors of coronary heart disease: the PRIME Study.

OBJECTIVE: This study was undertaken to examine the association of plasma inflammatory markers such as C-reactive protein (CRP), interleukin-6, and fibrinogen with the incidence of coronary heart disease within the prospective cohort study on myocardial infarction (PRIME study). **METHODS AND RESULTS:** Multiple risk factors were recorded at baseline in 9758 men aged 50 to 59 years who were free of coronary heart disease (CHD) on entry. Nested case-control comparisons were carried out on 317 participants who suffered myocardial infarction (MI)-coronary death (n=163) or angina (n=158) as an initial CHD event during a follow-up for 5 years. After adjustment for traditional risk factors, incident MI-coronary death, but not angina, was significantly associated with CRP, interleukin-6, and fibrinogen, but only interleukin-6 remained significantly associated with MI-coronary death when the 3 inflammatory markers were included in the model. The different interleukin-6 levels in Northern Ireland and France partly explained the difference in risk between these countries. Interleukin-6 appeared as a risk marker of MI-coronary death, and it improved the definition of CHD risk beyond LDL cholesterol. **CONCLUSIONS:** This association may reflect the underlying inflammatory reaction located in the atherosclerotic plaque or a genetic susceptibility on the part of CHD subjects to answer a proinflammatory stimulus and subsequent increase in hepatic CRP gene expression.

Arterioscler Thromb Vasc Biol . 2003 Jul 1;23(7):1255-61. Epub 2003 May 29

Relationship between interleukin 6 and mortality in patients with unstable coronary artery disease: effects of an early invasive or noninvasive strategy.

CONTEXT: Inflammatory activity is associated with high rates of long-term mortality in unstable coronary artery disease (CAD). Interleukin 6 (IL-6) induces C-reactive protein and fibrinogen, systemic markers of inflammation. **OBJECTIVES:** To determine whether plasma levels of IL-6 are predictive of mortality and to evaluate the interaction of IL-6 levels with the effects of invasive vs noninvasive treatment strategies in unstable CAD patients. **DESIGN, SETTING, AND PATIENTS:** The prospective, randomized Fragmin and Fast Revascularisation During Instability in Coronary Artery Disease II trial, conducted among 3,489 patients, 3,269 of whom had plasma samples analyzed for IL-6 levels, with diagnosed unstable CAD (67% male; median age, 67 years) at 58 Scandinavian hospitals between June 1996 and August 1998. **INTERVENTIONS:** Patients were randomly assigned to receive either an early invasive (n = 1222) or a noninvasive treatment strategy (n = 1235). The latter group, as well as 666 patients with contraindications to invasive therapy, were further randomized to 90-day treatment with low-molecular-weight heparin (dalteparin, 5000-7500 IU twice per day; n = 1140) or placebo (n = 1127). **MAIN OUTCOME MEASURE:** Mortality at 6 and 12 months in the medically and interventionally randomized cohorts, respectively, in relation to IL-6 levels, measured at randomization. **RESULTS:** Plasma levels of IL-6 that were at least 5 ng/L compared with levels lower than 5 ng/L were associated with greatly increased mortality in the noninvasive group (7.9% vs 2.3%; relative risk [RR], 3.47; 95% confidence interval [CI], 1.94-6.21) and in the placebo-treated group (7.9% vs 2.5%; RR, 3.19; 95% CI, 1.77-5.74). The association remained significant after adjustment for most established risk indicators. An early invasive treatment strategy strongly reduced 12-month mortality among those with elevated IL-6 levels (5.1% absolute reduction; P =.004) whereas mortality was not reduced among patients without elevated IL-6 concentrations. Those taking dalteparin with elevated IL-6 levels experienced lower 6-month mortality than those who did not take dalteparin (3.5% absolute reduction; P =.08). **CONCLUSIONS:** Circulating IL-6 is a strong independent marker of increased mortality in unstable CAD and identifies patients who benefit most from a strategy of early invasive management.

JAMA . 2001 Nov 7;286(17):2107-13

Dose effects of recombinant human interleukin-6 on pituitary hormone secretion and energy expenditure.

Interleukin-6 (IL-6), the main circulating cytokine, is putatively a major mediator of the effects of the immune system on several endocrine axes and intermediate metabolism. We performed dose-response studies of recombinant human IL-6 on pituitary hormone secretion in 15 healthy male volunteers, using 5 single, escalating subcutaneous doses of IL-6 (0.1, 0.3, 1.0, 3.0 and 10.0 micrograms/kg body weight), each in 3 volunteers. We measured resting metabolic rate (RMR) with indirect calorimetry and plasma anterior pituitary hormones and vasopressin (AVP) at baseline and half-hourly over 4 hours after the injection. All doses examined were tolerated well and produced no significant adverse effects. Dose-dependent RMR increases were observed in response to the 3.0- and 10.0-microgram/kg doses of IL-6, beginning at 60 min and slowly peaking between 180 and 240 min. Plasma adrenocorticotrophic-hormone concentrations increased dramatically and dose-dependently in all the patients who received the 3.0- and 10.0-microgram/kg doses of IL-6, respectively, peaking to 150 and 255 pg/ml at 60 min, and slowly

returning to normal by 4 hours. Corresponding plasma cortisol levels peaked dose-dependently between 90 and 150 min, but remained elevated throughout the sampling period. In contrast, the growth hormone (GH) dose-response was bell-shaped, with maximum (approximately 100-fold) stimulation achieved by 3.0 micrograms/kg IL-6. Prolactin (PRL) showed a similar but less pronounced response pattern. Thyroid-stimulating hormone (TSH) dose-dependently and progressively decreased over the 240 min, while gonadotropins showed no clear-cut changes. In conclusion, subcutaneous IL-6 administration induced synchronized dose-dependent increases in the RMR and hypothalamic-pituitary-adrenal axis activity, suggesting that hypothalamic corticotropin-releasing hormone may mediate both of these functions in humans. IL-6 also acutely stimulated GH and PRL secretion and suppressed TSH secretion. The dose of 3.0 micrograms/kg could be used safely in the study of patients with disturbances of the hypothalamic-pituitary unit or of thermogenesis.

Neuroendocrinology. 1997 Jul;66(1):54-62

Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events.

BACKGROUND: Both C-reactive protein and low-density lipoprotein (LDL) cholesterol levels are elevated in persons at risk for cardiovascular events. However, population-based data directly comparing these two biologic markers are not available. **METHODS:** C-reactive protein and LDL cholesterol were measured at base line in 27,939 apparently healthy American women, who were then followed for a mean of eight years for the occurrence of myocardial infarction, ischemic stroke, coronary revascularization, or death from cardiovascular causes. We assessed the value of these two measurements in predicting the risk of cardiovascular events in the study population. **RESULTS:** Although C-reactive protein and LDL cholesterol were minimally correlated ($r=0.08$), base-line levels of each had a strong linear relation with the incidence of cardiovascular events. After adjustment for age, smoking status, the presence or absence of diabetes mellitus, categorical levels of blood pressure, and use or nonuse of hormone-replacement therapy, the relative risks of first cardiovascular events according to increasing quintiles of C-reactive protein, as compared with the women in the lowest quintile, were 1.4, 1.6, 2.0, and 2.3 ($P<0.001$), whereas the corresponding relative risks in increasing quintiles of LDL cholesterol, as compared with the lowest, were 0.9, 1.1, 1.3, and 1.5 ($P<0.001$). Similar effects were observed in separate analyses of each component of the composite end point and among users and nonusers of hormone-replacement therapy. Overall, 77% of all events occurred among women with LDL cholesterol levels below 160 mg per deciliter (4.14 mmol per liter), and 46% occurred among those with LDL cholesterol levels below 130 mg per deciliter (3.36 mmol per liter). By contrast, because C-reactive protein and LDL cholesterol measurements tended to identify different high-risk groups, screening for both biologic markers provided better prognostic information than screening for either alone. Independent effects were also observed for C-reactive protein in analyses adjusted for all components of the Framingham risk score. **CONCLUSIONS:** These data suggest that the C-reactive protein level is a stronger predictor of cardiovascular events than the LDL cholesterol level and that it adds prognostic information to that conveyed by the Framingham risk score.

N Engl J Med. 2002 Nov 14;347(20):1557-65

The effect of N-acetylcysteine on nuclear factor-kappa B activation, interleukin-6, interleukin-8, and intercellular adhesion molecule-1 expression in patients with sepsis.

OBJECTIVE: Expression of inflammatory mediators is controlled in part at the transcriptional level via nuclear factor-kappa B. Inhibition of nuclear factor-kappa B activation may be beneficial in critically ill patients. N-acetylcysteine is an antioxidant that inhibits nuclear factor-kappa B activation in vitro. In this pilot study we investigated the effect of N-acetylcysteine on nuclear factor-kappa B activation and circulating cytokine and adhesion molecules in patients with sepsis. **DESIGN:** Prospective, randomized, double blind, placebo-controlled pilot trial. **SETTING:** Eight-bed intensive care unit in a university teaching hospital. **PATIENTS:** Twenty consecutive patients within 12 hrs of fulfilling the consensus criteria for sepsis. **INTERVENTIONS:** A bolus of 150 mg/kg N-acetylcysteine in 100 mL of 0.9% saline over 15 mins, then 50 mg/kg in 100 mL of 0.9% saline over 4 hours as a loading dose, and then a maintenance infusion of 50 mg/kg in 200 mL of 0.9% saline over each 24-hr period for a total of 72 hours, or an equivalent volume of saline. **MEASUREMENTS AND MAIN RESULTS:** Nuclear factor-kappa B activation was measured in mononuclear leukocytes using electrophoretic mobility shift assay, at baseline and 24, 48, 72, and 96 hours later. Activation decreased significantly in patients treated with N-acetylcysteine ($p=.016$) but not placebo and was significantly reduced at 72 hours compared with both preinfusion values ($p=.028$) and patients receiving placebo ($p=.01$). Plasma interleukin-6, interleukin-8, and soluble intercellular adhesion molecule-1 concentrations were measured using enzyme immunoassay. Interleukin-6 concentrations were high initially and then decreased in all patients, regardless of whether they received N-acetylcysteine or placebo. Interleukin-8 decreased significantly only in those who received N-acetylcysteine ($p=.0081$). Soluble intercellular adhesion molecule-1 concentrations remained unchanged in all patients. **CONCLUSIONS:** Administration of N-acetylcysteine results in decreased nuclear factor-kappa B activation in patients with sepsis, associated with decreases in interleukin-8 but not interleukin-6 or soluble intercellular adhesion molecule-1. These pilot data suggest that antioxidant therapy with N-acetylcysteine may be useful in blunting the inflammatory response to sepsis. Further studies are warranted.

Crit Care Med. 2003 Nov;31(11):2574-8

ABSTRACTS

Soy

Legumes and soybeans: overview of their nutritional profiles and health effects.

Legumes play an important role in the traditional diets of many regions throughout the world. In contrast in Western countries beans tend to play only a minor dietary role despite the fact that they are low in fat and are excellent sources of protein, dietary fiber, and a variety of micronutrients and phytochemicals. Soybeans are unique among the legumes because they are a concentrated source of isoflavones. Isoflavones have weak estrogenic properties and the isoflavone genistein influences signal transduction. Soyfoods and isoflavones have received considerable attention for their potential role in preventing and treating cancer and osteoporosis. The low breast cancer mortality rates in Asian countries and the putative antiestrogenic effects of isoflavones have fueled speculation that soyfood intake reduces breast cancer risk. The available epidemiologic data are limited and only weakly supportive of this hypothesis, however, particularly for postmenopausal breast cancer. The data suggesting that soy or isoflavones may reduce the risk of prostate cancer are more encouraging. The weak estrogenic effects of isoflavones and the similarity in chemical structure between soybean isoflavones and the synthetic isoflavone ipriflavone, which was shown to increase bone mineral density in postmenopausal women, suggest that soy or isoflavones may reduce the risk of osteoporosis. Rodent studies tend to support this hypothesis, as do the limited preliminary data from humans. Given the nutrient profile and phytochemical contribution of beans, nutritionists should make a concerted effort to encourage the public to consume more beans in general and more soyfoods in particular.

Am J Clin Nutr . 1999 Sep;70(3 Suppl):439S-450S

Effect of genistein on in vitro and in vivo models of cancer.

In two-thirds of studies on the effect of genistein-containing soy materials in animal models of cancer, the risk of cancer (incidence, latency or tumor number) was significantly reduced. In addition, purified genistein delayed mammary tumor appearance in association with increased cell differentiation in mammary tissue in rats treated with 7, 12-dimethylbenz[a]anthracene when administered neonatally, inhibited phorbol ester-induced H₂O₂ production in a model of skin cancer, and inhibited aberrant crypt formation in a model of colonic cancer. In in vitro models, genistein inhibited the proliferation of human tumor cell lines in culture with a wide variation in IC₅₀ values (2.6-79 μmol/L, or 1-30 micrograms/mL). In only a few cases was the IC₅₀ below 13.2 μmol/L (5 micrograms/mL), the presumed upper limit for the serum genistein concentration in those on a high soy diet. In future studies, greater emphasis should be placed on the effect of genistein on nontransformed, normal cell lines from the tissues where cancer can occur rather than established tumor cell lines. Similarly, the effect of genistein on the progression and/or promotion of cancer may be more clearly examined using nontransformed cell lines transfected with specific oncogenes thought to be activated during oncogenesis.

J Nutr . 1995 Mar;125(3 Suppl):777S-783S

The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation.

CONTEXT: Raloxifene hydrochloride is a selective estrogen receptor modulator that has antiestrogenic effects on breast and endometrial tissue and estrogenic effects on bone, lipid metabolism, and blood clotting. OBJECTIVE: To determine whether women taking raloxifene have a lower risk of invasive breast cancer. DESIGN AND SETTING: The Multiple Outcomes of Raloxifene Evaluation (MORE), a multicenter, randomized, double-blind trial, in which women taking raloxifene or placebo were followed up for a median of 40 months (SD, 3 years), from 1994 through 1998, at 180 clinical centers composed of community settings and medical practices in 25 countries, mainly in the United States and Europe. PARTICIPANTS: A total of 7,705 postmenopausal women, younger than 81 (mean age, 66.5) years, with osteoporosis, defined by the presence of vertebral fractures or a femoral neck or spine T-score of at least 2.5 SDs below the mean for young healthy women. Almost all participants (96%) were white. Women who had a history of breast cancer or who were taking estrogen were excluded. INTERVENTION: Raloxifene, 60 mg, 2 tablets daily; or raloxifene, 60 mg, 1 tablet daily and 1 placebo tablet; or 2 placebo tablets. MAIN OUTCOME MEASURES: New cases of breast cancer, confirmed by histopathology. Transvaginal ultrasonography was used to assess the endometrial effects of raloxifene in 1781 women. Deep vein thrombosis or pulmonary embolism were determined by chart review. RESULTS: Thirteen cases of breast cancer were confirmed among the 5,129 women assigned to raloxifene vs 27 among the 2,576 women assigned to placebo (relative risk [RR], 0.24; 95% confidence interval [CI], 0.13-0.44; P<.001). To prevent 1 case of breast cancer, 126 women would need to be treated. Raloxifene decreased the risk of estrogen receptor-positive breast cancer by 90% (RR, 0.10; 95% CI, 0.04-0.24), but not estrogen receptor-negative invasive breast cancer (RR, 0.88; 95% CI, 0.26-3.0). Raloxifene increased the risk of venous thromboembolic disease (RR, 3.1; 95% CI, 1.5-6.2), but did not increase the risk of endometrial cancer (RR, 0.8; 95% CI, 0.2-2.7). CONCLUSION: Among postmenopausal women with osteoporosis, the risk of invasive breast cancer was decreased by 76% during 3 years of treatment with raloxifene.

JAMA . 1999 Jun 16;281(23):2189-97

Dietary effects on breast-cancer risk in Singapore.

It is suspected that diet influences the risk of getting breast cancer. A study of diet and breast cancer was done among 200 Singapore Chinese women with histologically confirmed disease and 420 matched controls. A quantitative food-frequency questionnaire was used to assess intakes of selected nutrients and foods 1 year before interview. Daily intakes were computed and risk analysed after adjustment for concomitant risk factors. In premenopausal women, high intakes of animal proteins and red meat were associated with increased risk. Decreased risk was associated with high intakes of polyunsaturated fatty acids (PUFA), beta-carotene, soya proteins, total soya products, a high PUFA to saturated fatty acid ratio, and a high proportion of soya to total protein. In multiple analysis, the variables which were significant after adjustment for each other were red meat (p less than 0.001) as a predisposing factor, and PUFA ($p = 0.02$), beta-carotene ($p = 0.003$), and soya protein ($p = 0.02$) as protective factors. The analysis of dietary variables in postmenopausal women gave uniformly non-significant results. Our finding that soya products may protect against breast cancer in younger women is of interest since these foods are rich in phyto-oestrogens.

Lancet. 1991 May 18;337(8751):1197-200

Soy isoflavones--benefits and risks from nature's selective estrogen receptor modulators (SERMs).

Phytoestrogens have become one of the more topical areas of interest in clinical nutrition. These non-nutrient bioactive compounds are ubiquitous to the plant kingdom and possess a wide range of biological properties that contribute to the many different health-related benefits reported for soy foods and flaxseeds--two of the most abundant dietary sources of phytoestrogens. Reviewed is the recent knowledge related to their pharmacokinetics and clinical effects, focusing mainly on isoflavones that are found in high concentrations in soy foods. Arguments are made for considering soy isoflavones as natural selective estrogen receptor modulators (SERMs) based upon recent data of their conformational binding to estrogen receptors. Rebuttal is made to several key and important issues related to the recent concerns about the safety of soy and its constituent isoflavones. This article is not intended to be a comprehensive review of the literature but merely highlight recent research with key historical perspectives.

J Am Coll Nutr. 2001 Oct;20(5 Suppl):354S-362S; discussion 381S-383S

Phytoestrogen intake and endometrial cancer risk.

BACKGROUND: The development of endometrial cancer is largely related to prolonged exposure to unopposed estrogens. Phytoestrogens (i.e., weak estrogens found in plant foods) may have antiestrogenic effects. We evaluated the associations between dietary intake of seven specific compounds representing three classes of phytoestrogens (isoflavones, coumestans, and lignans) and the risk of endometrial cancer. **METHODS:** In a case-control study from the greater San Francisco Bay Area, we collected dietary information from 500 African American, Latina, and white women aged 35-79 years who were diagnosed with endometrial cancer between 1996 and 1999 and from 470 age- and ethnicity-matched control women identified through random-digit dialing. Unconditional logistic regression analyses were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs). **RESULTS:** Isoflavone (OR = 0.59, 95% CI = 0.37 to 0.93 for the highest versus lowest quartile of exposure) and lignan (OR = 0.68, 95% CI = 0.44 to 1.1) consumptions were inversely related to the risk of endometrial cancer. These associations were slightly stronger in postmenopausal women (OR = 0.44, 95% CI = 0.26 to 0.77 and OR = 0.57, 95% CI = 0.34 to 0.97 for isoflavones and lignans, respectively). Obese postmenopausal women consuming relatively low amounts of phytoestrogens had the highest risk of endometrial cancer (OR = 6.9, 95% CI = 3.3 to 14.5 compared with non-obese postmenopausal women consuming relatively high amounts of isoflavones); however, the interaction between obesity and phytoestrogen intake was not statistically significant. **CONCLUSION:** Some phytoestrogenic compounds, at the levels consumed in the typical American-style diet, are associated with reduced risk of endometrial cancer.

J Natl Cancer Inst. 2003 Aug 6;95(15):1158-64

ABSTRACTS

Vitamin B12

Homocyst(e)ine and cardiovascular disease: a critical review of the epidemiologic evidence.

PURPOSE: To review epidemiologic studies on the association between homocyst(e)ine level and risk for cardiovascular disease and the potential benefits of homocysteine-decreasing therapies. **DATA SOURCES:** Computerized and manual searches of the literature on total homocysteine levels and cardiovascular disease. **STUDY SELECTION:** Prospective studies and major retrospective epidemiologic studies evaluating the association between homocyst(e)ine levels and cardiovascular disease and the association between blood levels or dietary intake of folate, vitamin B6, and vitamin B12 and cardiovascular disease. **DATA EXTRACTION:** Relevant data on patient population, plasma homocyst(e)ine levels, duration of follow-up, and main results were extracted from studies that met the inclusion criteria. **DATA SYNTHESIS:** The designs and results of studies included in this review are summarized. A formal meta-analysis was not performed because the studies were heterogeneous in method and design. **CONCLUSIONS:** Results of epidemiologic studies suggest that moderately elevated plasma or serum homocyst(e)ine levels are prevalent in the general population and are associated with an increased risk for cardiovascular disease, independent of classic cardiovascular risk factors. Simple, inexpensive, nontoxic therapy with folic acid, vitamin B6, and vitamin B12 reduces plasma homocyst(e)ine levels. Although the association between homocyst(e)ine levels and cardiovascular disease is generally strong and biologically plausible, the data from the prospective studies are less consistent. In addition, epidemiologic observations of an association between hyperhomocyst(e)inemia and cardiovascular risk do not prove the existence of a causal relation. Therefore, the effectiveness of folate, vitamin B6, and vitamin B12 in reducing cardiovascular morbidity and mortality requires rigorous testing in randomized clinical trials. Several such trials are under way; their results may greatly affect cardiovascular morbidity and mortality, given the simplicity and low cost of vitamin therapy.

Ann Intern Med. 1999 Sep 7;131(5):363-75

Methionine synthase polymorphism is a risk factor for Alzheimer's disease.

Alzheimer's disease (AD) patients show increased plasma levels of homocysteine, whose conversion to methionine is catalyzed by methionine synthase (MS). Although altered MS activity may result from the MS A2756G polymorphism, the latter's possible association with AD remains unexplored. To assess whether the MS A2756G polymorphism holds any influence on AD risk, we have analyzed 172 AD patients and 166 controls. We have also investigated whether the MS-A or MS-G allele interacts with the APOE4 allele. Our results indicate that association with the MS-AA genotype is an APOE4 allele-independent risk factor for AD. These findings provide novel evidence implicating genetic enzymatic alterations of homocysteine metabolic pathways in the pathogenesis of AD.

Neuroreport. 2003 Jul 18;14(10):1391-4

Effect of homocysteine-lowering therapy with folic acid, vitamin B12, and vitamin B6 on clinical outcome after percutaneous coronary intervention: the Swiss Heart study: a randomized controlled trial.

CONTEXT: Plasma homocysteine level has been recognized as an important cardiovascular risk factor that predicts adverse cardiac events in patients with established coronary atherosclerosis and influences restenosis rate after percutaneous coronary intervention. **OBJECTIVE:** To evaluate the effect of homocysteine-lowering therapy on clinical outcome after percutaneous coronary intervention. **DESIGN, SETTING, AND PARTICIPANTS:** Randomized, double-blind placebo-controlled trial involving 553 patients referred to the University Hospital in Bern, Switzerland, from May 1998 to April 1999 and enrolled after successful angioplasty of at least 1 significant coronary stenosis (> or = 50%). **INTERVENTION:** Participants were randomly assigned to receive a combination of folic acid (1 mg/d), vitamin B12 (cyanocobalamin, 400 micro g/d), and vitamin B6 (pyridoxine hydrochloride, 10 mg/d) (n = 272) or placebo (n = 281) for 6 months. **MAIN OUTCOME MEASURE:** Composite end point of major adverse events defined as death, nonfatal myocardial infarction, and need for repeat revascularization, evaluated at 6 months and 1 year. **RESULTS:** After a mean (SD) follow-up of 11 (3) months, the composite end point was significantly lower at 1 year in patients treated with homocysteine-lowering therapy (15.4% vs 22.8%; relative risk [RR], 0.68; 95% confidence interval [CI], 0.48-0.96; P = .03), primarily due to a reduced rate of target lesion revascularization (9.9% vs 16.0%; RR, 0.62; 95% CI, 0.40-0.97; P = .03). A nonsignificant trend was seen toward fewer deaths (1.5% vs 2.8%; RR, 0.54; 95% CI, 0.16-1.70; P = .27) and nonfatal myocardial infarctions (2.6% vs 4.3%; RR, 0.60; 95% CI, 0.24-1.51; P = .27) with homocysteine-lowering therapy. These findings remained unchanged after adjustment for potential confounders. **CONCLUSION:** Homocysteine-lowering therapy with folic acid, vitamin B12, and vitamin B6 significantly decreases the incidence of major adverse events after percutaneous coronary intervention.

JAMA. 2002 Aug 28;288(8):973-9

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