

## STROKE (THROMBOTIC)

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## **Coffee consumption in hypertensive men in older middle-age and the risk of stroke: the Honolulu Heart Program.**

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J Clin Epidemiol (England) Jun 1998, 51 (6) p487-94

**OBJECTIVE:** To examine the association between coffee consumption and the development of stroke in men at high risk for cardiovascular disease.

**METHODS:** Coffee intake was observed from 1965 to 1968 in a cohort of men enrolled in the Honolulu Heart Program with follow-up for incident stroke over a 25-year period. Subjects were 499 hypertensive men (having systolic or diastolic blood pressures at or above 140 and 90 mm Hg, respectively) in older middle-age (55 to 68 years) when follow-up began. Past and current cigarette smokers were excluded from follow-up.

**RESULTS:** In the course of follow-up, 76 men developed a stroke. After age-adjustment, risk of thromboembolic stroke increased significantly with increases in coffee consumption ( $P = 0.002$ ). No relationships were observed with hemorrhagic stroke. When adjusted for other factors, the risk of thromboembolic stroke was more than doubled for men who consumed three cups of coffee per day as compared to nondrinkers of coffee ( $RR = 2.1$ ; 95%  $CI = 1.2-3.7$ ).

**CONCLUSIONS:** Although in need of further confirmation, consumption of coffee appears to be positively associated with an increased risk of thromboembolic stroke in hypertensive men in older middle-age. Findings suggest that it may be prudent to advise older middle-aged men with hypertension who consume large amounts of coffee to consider reducing their coffee intake.

## **The white blood cell and plasma fibrinogen in thrombotic stroke. A significant correlation.**

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University Department of Medicine, Ninewells Hospital & Medical School, Dundee, Scotland.  
Int Angiol (Italy) Jun 1998, 17 (2) p120-4

**OBJECTIVES:** Thrombotic stroke is a common disorder with considerable mortality and morbidity. Risk factors for stroke include cigarette smoking, hypertension and hyperlipidaemia and these have been linked to abnormalities of haemorrhology and coagulation such as increased fibrinogen. Other haemorrhological abnormalities have also been documented. These include an elevation in the white blood cell (WBC) count. The aim of our study was to evaluate plasma fibrinogen, WBC aggregation and the release of free radicals in thrombotic stroke.

**EXPERIMENTAL DESIGN:** Thirty-four patients with thrombotic stroke were enrolled in the study. The data were compared to 58 matched controls.

**SETTING:** This study was carried out in Ninewells Hospital, Dundee on patients previously admitted to the medical wards with acute stroke.

**MEASURES:** Plasma fibrinogen, WBC aggregation and plasma malondialdehyde (MDA) were measured in this study.

**RESULTS:** As expected, the stroke patients have a significantly higher fibrinogen level ( $4.3 \pm 1.2$  g/dl versus  $3.1 \pm 0.6$ ,  $p < 0.001$ ). WBC aggregation is also increased in the patient group ( $47.5 \pm 10.4\%$  versus  $42.7 \pm 10.6$ ,  $p = 0.036$ ), as is plasma MDA ( $8.6 \pm 2.0$  micromol/l versus  $7.1 \pm 1.07$ ,  $p < 0.001$ ). The factor VIII von Willebrand factor antigen measured as a marker as vascular damage was also significantly higher in the patient group ( $251 \pm 87\%$  versus  $182 \pm 64$ ,  $p < 0.001$ ). There was also a statistically significant correlation between fibrinogen level and WBC aggregation, and fibrinogen and MDA. These are both statistically significant  $p = 0.012$  and  $p < 0.001$  respectively.

**CONCLUSIONS:** We believe our study suggests that enhanced WBC aggregation/adhesion with release of free radicals may be another mechanism whereby fibrinogen exerts its known detrimental effect in stroke development. This may allow planning of therapeutic strategies as yet undeveloped.

## **Elevated serum glycosaminoglycans with hypomagnesemia in patients with coronary artery disease & thrombotic stroke.**

Kumari KT; Augustine J; Leelamma S; Kurup PA; Ravikumar A; Sajeesh K; Eapen S; Nair AR; Vijayalekshmi N; Karthikeyan S; et al  
Department of Biochemistry, University of Kerala.  
Indian J Med Res (India) Mar 1995, 101 p115-9

Elevated levels of serum glycosaminoglycans (GAG), associated with hypomagnesemia were observed in patients of proven CAD and thrombotic stroke in Kerala. Serum lipid profile was normal in the majority of these patients, indicating that elevated serum GAG may be an even more reliable indicator of atherosclerosis than elevated serum total cholesterol or LDL cholesterol. Autopsy samples of carotid artery and aorta which had atheroma showed significantly higher GAG when compared to samples which showed no atheroma. Serum Mg levels were significantly lower in CAD and thrombotic stroke patients as compared to controls. Mg deficiency may be one of the factors involved in the increased level of GAG.

## **Serum lipids and lipoprotein abnormalities in patients with thrombotic stroke--with exploring the protective role of HDL subfractions.**

Shieh SM; Shen MM; Tsai WJ; Shiu LR; Wang DJ  
Proc Natl Sci Counc Repub China [B] (Taiwan) Oct 1985, 9 (4) p298-304

The main purpose of this report is to demonstrate the presence of subfractions in serum HDL and to explore their role in the pathogenesis of thrombotic stroke. Preparative ultracentrifugation was used to isolate the differing density fractions of serum lipoproteins, and 2-27% polyacrylamide gradient gel electrophoresis was used to identify the character of the HDL subfractions. The study was performed on 59 Chinese males, in whom 31 were patients with thrombotic stroke affecting the cerebral cortex diagnosed by neurological examination and computed tomography; and the others grouped as healthy control. The age and Broca index of both groups were similar. The serum levels of total cholesterol and LDL-cholesterol were normal. However, in the thrombotic stroke group HDL-cholesterol was significantly lower and correlated inversely with both significantly higher levels of VLDL-cholesterol ( $r=-0.5392$ ,  $p$  less than 0.01) and VLDL-triglyceride ( $r=-0.5866$ ,  $p$  less than 0.01). The serum levels of total triglycerides and LDL-triglyceride were also significantly higher in patient with thrombotic stroke. The mean area percentage of HDL<sub>2b</sub> subfraction measured in the diameter range as determined by gradient gel electrophoresis was significantly lower and HDL<sub>2</sub> also showed the same tendency in patients with thrombotic stroke. Our finding was consistent with the postulation that HDL<sub>2</sub> or HDL<sub>2b</sub> in particular, probably played a more protective role than any other HDL subfractions against thrombotic stroke, one of the major atherosclerotic complications.

## **Effect of piracetam on recovery and rehabilitation after stroke: a double-blind, placebo-controlled study.**

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Clin Neuropharmacol 1994 Aug;17(4):320-31

The nootropic agent piracetam has been shown to improve learning and memory, and it may, by this means, facilitate recovery and rehabilitation after a stroke. We report the results of a pilot study exploring its effects in patients undergoing rehabilitation after acute cerebral infarction in the carotid artery territory. We compared piracetam and placebo, each given for 12 weeks, in a multicenter, double-blind, randomized trial of parallel-group design; testing was performed at baseline (6-9 weeks poststroke), weeks 5 and 12, and, in fewer patients, 12 weeks after termination of treatment. Standardized tests of activities of daily living (Barthel Index, Kuriansky Test), aphasia (Aachen Aphasia Test), and perception (Rivermead Perception Assessment Battery) were the primary efficacy variables. Of 158 patients, 137 (81 males, 56 females) were studied after treatment and 88 at 24-week follow-up. Thirty patients on piracetam (45%) and 37 on placebo (53%) were aphasic on entry. Both groups, including the subgroups with aphasia, were well matched at baseline for demographic data, stroke sequelae, type and severity of aphasia, and prognostic parameters. Multivariate analysis of Aachen Aphasia subtest scores showed a significant overall improvement relative to baseline in favor of piracetam ( $p = 0.02$ ) at 12 weeks. This was not seen at 24 weeks when, however, fewer patients were available for evaluation so that we could neither confirm nor deny whether improvement was maintained after cessation of piracetam. We were unable to demonstrate an effect on tests of activities of daily living and could neither confirm nor exclude an effect on perceptual deficit. We have shown an improvement in aphasia in patients undergoing rehabilitation after a stroke after 12 weeks' treatment

with piracetam that requires confirmation in further studies.

## **The role of piracetam in the treatment of acute and chronic aphasia.**

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Pharmacopsychiatry 1999 Mar;32 Suppl 1:38-43

Piracetam has been shown to improve speech in aphasic patients. This paper reviews the evidence for this benefit in aphasic patients with acute stroke and, in conjunction with language treatment, in post-acute and chronic aphasia. Early double-blind, placebo-controlled trials in acute stroke showed improvement in several neurologic parameters including aphasia. Subsequently two randomized double-blind placebo-controlled studies were performed which utilised the Aachen Aphasia Test (AAT), a validated and standardized procedure, to assess language function. Patients received placebo or piracetam 4.8g daily for 12 weeks in one study and for 6 weeks in the other. In both studies patients received concomitant intensive speech therapy; one included patients 6-9 weeks after stroke while in the other the duration of aphasia varied between 4 weeks and 3 years. Compared with placebo there was improvement in both studies on piracetam in all 5 subtests of the AAT and significant overall improvement in aphasia. This indicated that, given in conjunction with language therapy, piracetam improved speech in patients with post-acute and chronic aphasia. In the Piracetam in Acute Stroke Study (PASS), of 927 patients treated within 12 hours of the onset of acute ischemic stroke, 373 were aphasic. Treatment consisted of placebo or an intravenous bolus of 12g piracetam, 12g piracetam daily for 4 weeks and 4.8 g daily for a further 8 weeks. After 12 weeks significantly more patients (approximately 10%,  $P=0.04$ ) had recovered from aphasia on piracetam than placebo while in 197 patients treated within 7 hours of stroke onset, the difference in favor of piracetam was 16% ( $P= 0.02$ ). These studies indicate that piracetam improves aphasia in acute stroke and, as an adjuvant to language therapy, in post-acute and chronic aphasia.

## **The clinical safety of high-dose piracetam--its use in the treatment of acute stroke.**

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Pharmacopsychiatry 1999 Mar;32 Suppl 1:33-7

Recent post-marketing surveillance reports have confirmed the benign safety profile and lack of organ toxicity shown by piracetam during its 25 years of clinical usage. Tolerance has proved equally good with the more recent use of larger doses (up to 24 g/day) for the long-term control of cortical myoclonus and when given intravenously to patients with acute stroke. This paper provides a brief review of these findings and records the safety of piracetam as found in the Piracetam in Acute Stroke Study (PASS), a randomized multicenter placebo-controlled study in 927 patients with acute ischemic stroke. Patients receive one intravenous bolus injection of placebo or 12 g piracetam, piracetam 12 g daily for 4 weeks and maintenance treatment for 8 weeks. The major results have been reported (De Deyn et al., Stroke 28 [1997] 2347-2352). Safety was assessed taking into account adverse events including abnormal laboratory test results and mortality. Death within 12 weeks occurred more frequently in the piracetam group but the difference from placebo was not significant. Of many potential risk, prognostic and treatment-related factors examined by logistic regression, 6 contributed significantly to death of which the most important were initial severity of stroke and age. Neither treatment nor any treatment-related factor contributed significantly to death. Adverse events were similar in frequency, type and severity in piracetam and placebo groups. Events of cerebral, non-cerebral and uncertain origin likewise occurred with similar frequency. Few patients discontinued because of adverse events. There was no difference between treatments in the frequency of events associated with bleeding, including hemorrhagic transformation of infarction. An important finding was that, of 31 patients with primary hemorrhagic stroke enrolled, 3 piracetam-treated patients died compared with 6 on placebo. The results suggest that piracetam in high dosage may be given to patients with acute stroke without significant adverse effects.

## **Neuroprotective therapy.**

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Semin Neurol 1998;18(4):485-92

The concept of neuroprotection relies on the principle that delayed neuronal injury occurs after ischemia. The phenomenon of the "ischemic cascade" has been described, and each step along this cascade provides a target for therapeutic intervention. In animal

models of global and focal cerebral ischemia, numerous preclinical studies have demonstrated various agents to be neuroprotective at different steps along this cascade. A wide variety of drugs has also been studied in humans. Ten classes of neuroprotective agents have reached phase III efficacy trials but have shown mixed results. They include calcium channel antagonists, NMDA receptor antagonists, lubeluzole, CDP-choline, the free radical scavenger tirilizad, anti-intercellular adhesion molecule-1 (ICAM-1) antibody, GM-1 ganglioside, clomethiazole, the sodium channel antagonist fosphenytoin, and piracetam. In the future, clinicians may have an armamentarium of treatments for acute ischemic stroke at their disposal, with a combination of agents directed at different sites in the ischemic cascade being the ultimate goal.

## **Acute treatment of stroke. PASS group. Piracetam Acute Stroke Study.**

De Deyn PP, Orgogozo JM, De Reuck J  
Lancet 1998 Jul 25;352(9124):326

No abstract.

## **[Piracetam treatment in ischemic stroke].**

Tomczykiewicz K, Domzal T  
Kliniki Neurologicznej Centralnego Szpitala Klinicznego Wojskowej Akademii Medycznej, Warszawie.  
Neurol Neurochir Pol 1997 Nov-Dec;31(6):1101-9  
Comment on Lancet 1998 May 16;351(9114):1447-8

The increase of interest in piracetam in the treatment of stroke has been noticed lately. The reason of that is the unique double-action of this drug which depends on: 1. its effect on vascular system, and 2. improving of the metabolic process in a nerve cell. The purpose of our work was the evaluation of the therapeutic action of piracetam in comparison with other drugs, which are applied in treating stroke. 171 patients were examined, and piracetam was given to 40 of them. The effects of the treatment were evaluated after 14 days of using piracetam in dose of 12.0 g i.v. The authors estimate, that this drug is efficient in ischaemic stroke. However, its definite superiority over other drugs has not been firmly stated.

## **Treatment of acute ischemic stroke with piracetam. Members of the Piracetam in Acute Stroke Study (PASS) Group.**

De Deyn PP, Reuck JD, Deberdt W, Vlietinck R, Orgogozo JM  
Department of Neurology, Middelheim Hospital, Antwerp, Belgium.  
Stroke 1997 Dec;28(12):2347-52

**BACKGROUND AND PURPOSE:** Piracetam, a nootropic agent with neuroprotective properties, has been reported in pilot studies to increase compromised regional cerebral blood flow in patients with acute stroke and, given soon after onset, to improve clinical outcome. We performed a multicenter, randomized, double-blind trial to test whether piracetam conferred benefit when given within 12 hours of the onset of acute ischemic stroke to a large group of patients.

**METHODS:** Patients received placebo or 12 g piracetam as an initial intravenous bolus, 12 g daily for 4 weeks and 4.8 g daily for 8 weeks. The primary end point was neurologic outcome after 4 weeks as assessed by the Orgogozo scale. Functional status at 12 weeks as measured by the Barthel Index was the major secondary outcome. CT scan was performed within 24 hours of the onset of stroke but not necessarily before treatment. Analyses based on the intention to treat were performed in all randomized patients (n = 927) and in an "early treatment" population specified in the protocol as treatment within 6 hours of the onset of stroke but subsequently redefined as less than 7 hours after onset (n = 452).

**RESULTS:** In the total population, outcome was similar with both treatments (the mean Orgogozo scale after 4 weeks: piracetam 57.7, placebo 57.6; the mean Barthel Index after 12 weeks: piracetam 55.8, placebo 53.1). Mortality at 12 weeks was 23.9% (111/464) in the piracetam group and 19.2% (89/463) in the placebo group (relative risk 1.24, 95% confidence interval, 0.97 to 1.59; P = .15). Deaths were fewer in the piracetam group in those patients in the intention-to-treat population admitted with primary hemorrhagic stroke. Post hoc analyses in the early treatment subgroup showed differences favoring piracetam relative to placebo in mean Orgogozo scale scores after 4 weeks (piracetam 60.4, placebo 54.9; P = .07) and Barthel Index scores at 12 weeks

(piracetam 58.6, placebo 49.4;  $P = .02$ ). Additional analyses within this subgroup, confined to 360 patients with moderate and severe stroke (initial Orgogozo scale score  $< 55$ ), showed significant improvement on piracetam in both outcomes ( $P < .02$ ).

**CONCLUSIONS:** Piracetam did not influence outcome when given within 12 hours of the onset of acute ischemic stroke. Post hoc analyses suggest that piracetam may confer benefit when given within 7 hours of onset, particularly in patients with stroke of moderate and severe degree. A randomized, placebo-controlled, multicenter study, the Piracetam Acute Stroke Study II (PASS II) will soon begin.

## **[Factors influencing the prescribing of nootropic drugs. Results of a representative inquiry in Lower Saxony].**

[Article in German]

Stoppe G, Sandholzer H, Staedt J, Kiefer J, Winter S, Kochen MM, Ruther E  
Psychiatrische Klinik und Poliklinik, Universitat Gottingen.  
Dtsch Med Wochenschr 1995 Nov 24;120(47):1614-9

**AIM OF INVESTIGATION:** To discover (1) to what extent patients' wishes and the extent of any abnormality of brain performance influence the frequency with which "nootropic" drugs (those thought to affect brain activity, e.g. piracetam, pyritinol, or improve cerebral circulation, e.g. xanthine derivatives, Ginkgo biloba, secale alkaloids, calcium antagonists) are prescribed; (2) the medical practitioner's expectations of the effectiveness of such medications.

**METHOD:** In a personal interview, 145 family doctors and 14 neurologists in private practice in the Gottingen area of Germany (participation rate: 83.2% of those asked to participate) were questioned about fictitious cases (case 1: mild memory problem with or without expressed wish for medication; case 2: moderate dementia, of Alzheimer or multi-infarct type). The previously arranged interviews, which took place in the doctors' practice rooms, consisted of standardized open questions to the written case reports.

**RESULTS:** Regardless of the wish of the patient and the extent and type of the abnormal brain function about 70% of all participating doctors would prescribe those drugs, even though about 56% had doubts about their effectiveness. About 28% expected a positive effect on brain performance. A nearly equal proportion of doctors would continue an existing drug regimen as would prescribe one.

**CONCLUSION:** The prescription of the named group of drugs is influenced less by medical criteria than by factors which concern doctor-patient relationship.

## **tPA in acute ischemic stroke: United States experience and issues for the future.**

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Neurology 1998 Sep;51(3 Suppl 3):S53-5

The approval of tissue plasminogen activator (tPA) for treatment of patients with ischemic stroke in the United States marked the first therapy proven to reverse or limit the effects of an acute stroke. Despite this approval and the lack of an alternative therapy, the use of tPA in stroke has been quite low. Several explanations for this underutilization have been identified, including lack of patient awareness, potential complications, infrastructure deficiencies, and physician concerns. This article explores these issues and suggests strategies for improving the use of tPA as an acute therapy in stroke.

## **Secondary stroke prevention with low-dose aspirin, sustained release dipyridamole alone and in combination.**

ESPS Investigators.  
European Stroke Prevention Study. Forbes CD University of Dundee Medical School, Scotland, United Kingdom.  
Thromb Res 1998 Sep 15;92(1 Suppl 1):S1-6

Patients who had survived a stroke or transient ischaemic attacks (TIA) were admitted to a trial of low-dose aspirin (50 mg) alone,

sustained release dipyridamole (400 mg/day) alone, or a combination of the two agents, and results compared with a placebo over 24 months. This low-dose aspirin regimen produced in pairwise comparisons a significant risk reduction of 18% for stroke, 13% for stroke and/or death but no reduction in all cause mortality. The sustained release dipyridamole produced a significant risk reduction of 16% for stroke, 15% for stroke and/or death but no significant reduction of mortality. In combination, aspirin and dipyridamole produced a risk reduction of 37% in stroke, 24% in stroke and/or death, and no reduction in mortality. Similar findings were found in TIA, which was a secondary endpoint. These results are highly significant in comparison with placebo. As expected, there were enhanced reports of alimentary side-effects in the aspirin groups and also enhanced bleeding. Dipyridamole was associated with a slight increase in headache, which resolved in most patients if therapy was continued. The conclusions are that 50 mg/day of aspirin alone or 400 mg/day of sustained release dipyridamole alone are equally effective in stroke and TIA prevention. When used in combination the effects were additive and were significantly more effective than the single agents.

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### **Maternal infusion of antioxidants (Trolox and ascorbic acid) protects the fetal heart in rabbit fetal hypoxia**

Tan S, Liu YY, Nielsen VG, Skinner K, Kirk KA, Baldwin ST, Parks DA  
 Department of Pediatrics, School of Medicine, University of Alabama at Birmingham, 35233-7335, USA.  
 Division of Neonatology, 525 NHB, Birming (USA), 1996, 39/3 (499-503)

The antioxidants, Trolox (6-hydroxy-2,5,7,8-tetramethylchroman-2 carboxylic acid, a water soluble analog of vitamin E) and ascorbic acid (AA), protect the heart from ischemia-reperfusion injury. We hypothesized that maternal infusion of Trolox and AA, would reduce the fetal bradycardia and myocardial damage observed in fetal hypoxia and increase the total antioxidant activity in fetal plasma. Either i.v. saline (control group) or Trolox + AA (drug group) was randomly administered to 29 d-old pregnant rabbits. Fetal hypoxia was induced by uterine ischemia. Fetal heart rate, plasma CK-MB activity, and plasma total radical antioxidant potential (TRAP) were measured in different sets of animals. Fetal heart rate in the drug group was higher than in the control group for the first 35 min ( $p < 0.05$  at every 5-min interval). Fetal bradycardia ( $<60$  beats/min) occurred after 39 min (median) in the drug group, and 29 min in the control group ( $p < 0.05$ ). After 50 min of hypoxia, plasma CK-MB was lower in the drug group, 1204 plus or minus 132 U/L (mean plus or minus SEM), than in the control group, 2633 plus or minus 233 U/L ( $p < 0.05$ ), TRAP was higher in the drug group, 3.01 plus or minus 0.15 mM (Trolox equivalent concentration), than in the control group, 1.48 plus or minus 0.27 mM ( $p < 0.05$ ). Higher TRAP levels (greater than or equal to 2.0 mM) were associated with lower CK-MB levels ( $<2500$  U/L) ( $p < 0.05$ ). Administration of Trolox and AA to the mother has a beneficial effect on fetal myocardial damage after fetal hypoxia, and a small beneficial effect on fetal bradycardia during hypoxia. The beneficial effect may be due to the augmentation of fetal plasma antioxidants from maternal antioxidant pretreatment.

### **Amphiphilic alpha-tocopherol analogues as inhibitors of brain lipid peroxidation.**

Bolkenius FN, Verne-Mismer J, Wagner J, Grisar JM  
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 FrankBolkenius@mmd.com  
 Eur J Pharmacol (Netherlands) Feb 29 1996, 298 (1) p37-43

Neurological disorders, such as stroke, trauma, tardive dyskinesia, Alzheimer's and Parkinson's diseases, may be partially attributed to excessive exposition of the nervous tissue to oxygen-derived radicals. A novel water-soluble alpha-tocopherol analogue, 2,3-dihydro-2,2,4,6,7-pentamethyl-3-methylpiperazino methyl-1-benzofuran-5-yl dihydrochloride (MDL), is a potent radical scavenger. Following subcutaneous administration to mice, MDL inhibited the lipid peroxidation induced in the 100-fold diluted brain homogenates, with an ID<sub>50</sub> of 8 mg/kg. Rapid brain penetration, within 30-60 min postadministration, and even distribution into different brain areas were observed. MDL was also detected after oral administration. In brain homogenate undergoing lipid peroxidation, MDL prevented the consumption of an equal amount of alpha-tocopherol, while inhibiting the concomitant malondialdehyde formation. The radical scavenging capacity of MDL was superior to that of alpha-tocopherol, although

the peak and half-peak potentials were not significantly different. However, MDL was much less lipophilic, the partition coefficient (log P) at the octanol/water interface being 1.91. Although it is yet unknown, whether the applied criteria sufficiently predict its usefulness, beneficial effects of MDL may be expected in the above mentioned disorders.

### **Vitamin E plus aspirin compared with aspirin alone in patients with transient ischemic attacks**

Steiner M, Glantz M, Lekos A

Division of Hematology/Oncology, Memorial Hospital of Rhode Island, Pawtucket, USA.

Am J Clin Nutr 1995 Dec;62(6 Suppl):1381S-1384S

One hundred patients with transient ischemic attacks, minor strokes, or residual ischemic neurologic deficits were enrolled in a double-blind, randomized study comparing the effects of aspirin plus vitamin E (0.4 g (400 IU)/d; n = 52) with aspirin alone (325 mg; n = 48). The patients received study medication for 2 y or until they reached a termination point. Preliminary results show a significant reduction in the incidence of ischemic events in patients in the vitamin E plus aspirin group compared with patients taking only aspirin. There was no significant difference in the incidence of hemorrhagic stroke although both patients who developed it were taking vitamin E. Platelet adhesion was also measured in a randomized subgroup of both study populations by using collagen III as the adhesive surface. There was a highly significant reduction in platelet adhesiveness in patients who were taking vitamin E plus aspirin compared with those taking aspirin only. Measurement of alpha-tocopherol concentrations confirmed compliance of the patients with the medication schedule, showing a near doubling of serum concentrations of alpha-tocopherol. We concluded that the combination of vitamin E and a platelet antiaggregating agent (eg, aspirin) significantly enhances the efficacy of the preventive treatment regimen in patients with transient ischemic attacks and other ischemic cerebrovascular problems.

### **Poor plasma status of carotene and Vitamin-C is associated with higher mortality from ischemic heart disease and stroke: Basel Prospective Study**

Gey KF, Stahelin HB, Eichholzer M

Vitamin-Forschungseinheit and Reference Centre for Vitamins, WHO/MONICA Project, Universitat Bern.

Clin. Invest. (Germany), 1993, 71/1 (3-6)

Previous cross-cultural comparisons of the mortality from ischemic heart disease in European communities with associated plasma levels of essential antioxidants have revealed strong inverse correlations for vitamin E and relatively weak correlations for other antioxidants. Similarly, in a case-control study in Edinburgh low plasma levels of vitamin E were significantly associated with an increased risk of previously undiagnosed angina pectoris whereas low levels of other essential antioxidants lacked statistical significance. The current Basel Prospective Study is particularly well suited to elucidate the impact of antioxidants other than vitamin E. In this population (which was recently evaluated regarding cancer mortality) the plasma levels of vitamins E and A are exceptionally high and above the presumed threshold level of risk for ischemic heart disease. The present 12-year follow-up of cardiovascular mortality in this study reveals a significantly increased relative risk of ischemic heart disease and stroke at initially low plasma levels of carotene (< 0.23 micromol/l) and/or Vitamin-C (< 22.7 micromol/l), independently of vitamin E and of the classical cardiovascular risk factors. Low levels of both carotene and vitamin C increase the risk further, in the case of stroke even with significance for overmultiplicative interaction. In conclusion, in cardiovascular disease independent inverse correlations may exist for every major essential antioxidant although the latter can also interact synergistically. Therefore future intervention trials of antioxidants in the prevention of ischemic heart disease should primarily test the simultaneous optimization of the status of all principal essential antioxidants.

### **Neuroprotective properties of Ginkgo biloba - Constituents**

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Z. Phytother. (Germany), 1994, 15/2 (92-96)

More than 10 years ago it has been demonstrated, that an extract of the leaves of Ginkgo biloba (EGb 761) clearly increased the local cerebral blood flow and the tolerance against hypoxia in rats and mice. Using various models of cerebral ischemia and cultured neurons in vitro ginkgolides A and B as well as bilobalide were shown to be neuroprotective. The ginkgolides are known to be antagonists of the platelet activating factor (PAF) and this activity could be responsible for their neuroprotective potency. Bilobalide reduced the infarct size after focal cerebral ischemia of mice and rats more efficaciously than the ginkgolides A and B

and was capable of protecting neurons and astrocytes against damage, however, its mechanism of action however is still unknown.

### **Efficiency of ginkgo biloba extract (EGb 761) in antioxidant protection against myocardial ischemia and reperfusion injury**

Shen JG, Zhou DY

Department of Chinese Medicine, First Military Medical University, Guangzhou, China.  
Biochemistry and Molecular Biology International (Australia), 1995, 35/1 (125-134)

The cardio-protective mechanisms of EGb 761, an extract of Ginkgo biloba leaves, on myocardial ischemia reperfusion injury were investigated using rabbits subjected to 30 minutes of regional cardiac ischemia and 120 min of reperfusion under anesthesia. Compared to the saline perfused group, Egb 761 treatment (10 mg/kg, injected into the coronary artery) significantly inhibited the increase in lipid peroxidation and maintained total and CuZn-SOD levels in both plasma and tissue during and at the end of reperfusion. Both the decrease in tissue type plasminogen activator (t-PA) and the increase in plasminogen activator inhibitor-1 (PAI-1) caused by ischemia-reperfusion were also significantly suppressed by EGb 761 treatment. Furthermore, the ultrastructure of the myocytes of the EGb 761 treated heart was slightly damaged after ischemia-reperfusion, while the control ischemic-reperfused hearts demonstrated severe histological damages such as swelling and vacuolization of the mitochondria. These results suggest that EGb 761 protects hearts by its antioxidant properties and by its ability to adjust fibrinolytic activity.

### **Magnesium content of erythrocytes in patients with vasospastic angina**

Tanabe K, Noda K, Mikawa T, Murayama M, Sugai J

Second Department of Internal Medicine, St. Marianna University, School of Medicine, Kanagawa, Japan.  
Cardiovasc. Drugs Ther. (USA), 1991, 5/4 (677-680)

The possibility that a magnesium deficiency might be the underlying cause of vasospastic angina (VA) and the efficacy of Mg administration in its treatment were studied. Subjects included 15 patients with VA and 18 healthy subjects as the control group. The erythrocyte Mg content was measured by atomic absorption, and serum Mg was measured by conventional chemical assay. The efficacy of Mg administration was studied in seven patients with VA. The results were as follows: (a) The mean erythrocyte Mg content was less in the group with frequent episodes of angina (1.59 plus or minus 0.11 mg/dl) than in the group without angina (2.11 plus or minus 0.38 mg/dl,  $p < 0.01$ ) and in the control group (2.22 plus or minus 0.29 mg/dl,  $p < 0.01$ ). There was no significant difference between the control group and patients of each group with respect to serum Mg. (b) Coronary arterial spasm was induced by ergonovine maleate in seven patients and was completely inhibited by the administration of Mg sulfate (40-80 mEq, hourly) in six of these patients; in the remaining patient neither obvious ST change nor chest pain occurred. Thus, it was concluded that the measurement of erythrocyte Mg content is useful to determine how easily vasospasm might occur in VA and that the administration of Mg might be developed as a new therapy for spasm associated with a low erythrocyte Mg content.

### **Neuroprotective properties of Ginkgo biloba - Constituents**

Z. Phytother. (Germany), 1994, 15/2 (92-96)

More than 10 years ago it has been demonstrated, that an extract of the leaves of Ginkgo biloba (EGb 761) clearly increased the local cerebral blood flow and the tolerance against hypoxia in rats and mice. Using various models of cerebral ischemia and cultured neurons in vitro ginkgolides A and B as well as bilobalide were shown to be neuroprotective. The ginkgolides are known to be antagonists of the platelet activating factor (PAF) and this activity could be responsible for their neuroprotective potency. Bilobalide reduced the infarct size after focal cerebral ischemia of mice and rats more efficaciously than the ginkgolides A and B and was capable of protecting neurons and astrocytes against damage, however, its mechanism of action however is still unknown.

### **Variant angina due to deficiency of intracellular magnesium**

Tanabe K, Noda K, Kamegai M, Miyake F, Mikawa T, Murayama M, Sugai J

Second Department of Internal Medicine, St. Marianna University School of Medicine, Kanagawa, Japan.

A 51-year-old man was diagnosed as having variant angina by documentation of typical ST elevation during anginal attack and also by showing coronary arterial spasm (#2 and #12) during hyperventilation on coronary arteriography. Large quantities of calcium blocking agents and nitrates could not improve his symptoms. Lack of intracellular magnesium was suspected from a daily excretion of urine magnesium (5.3 mEq) and magnesium tolerance test (56.7%). After hourly infusion of magnesium sulfate (80 mEq), coronary spasm could not be induced by ergonovine.

### **Magnesium and sudden death**

Leary WP, Reyes AJ  
S. Afr. Med. J. (South Africa), 1983, 64/18 (697-698)

Magnesium deficiency may result from reduced dietary intake of the ion increased losses in sweat, urine or faeces. Stress potentiates magnesium deficiency, and an increased incidence of sudden death associated with ischaemic heart disease is found in some areas in which soil and drinking water lack magnesium. Furthermore, it has been demonstrated experimentally that reduction of the plasma magnesium level is associated with arterial spasm. Careful studies are required to assess the clinical importance of magnesium and the benefits of magnesium supplementation in man.

### **Magnesium deficiency produces spasms of coronary arteries: Relationship to etiology of sudden death ischemic heart disease**

Turlapaty PD, Altura BM  
Science (USA), 1980, 208/4440 (198-200)

Isolated coronary arteries from dogs were incubated in Krebs-Ringer bicarbonate solution and exposed to normal, high, and low concentrations of magnesium in the medium. Sudden withdrawal of magnesium from the medium increased whereas high concentrations of magnesium decreased the basal tension of the arteries. The absence of magnesium in the medium significantly potentiated the contractile responses of both small and large coronary arteries to norepinephrine, acetylcholine, serotonin, angiotensin, and potassium. These data support the hypothesis that magnesium deficiency, associated with sudden death ischemic heart disease, produces coronary arterial spasm.

### **Effect of vitamin E on hydrogen peroxide production by human vascular endothelial cells after hypoxia/reoxygenation**

Martin A, Zulueta J, Hassoun P, Blumberg JB, Meydani M  
Antioxidant Research Laboratory, Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA, USA.  
Free Radical Biology and Medicine (USA), 1996, 20/1 (99-105)

Changes in oxidative stress status play an important role in tissue injury associated with ischemia-reperfusion events such as those that occur during stroke and myocardial infarction. Endothelial cells (EC) from human saphenous vein and aorta were incubated for 22 h and found to take up vitamin E from media containing 0-60 mM vitamin E in a dose-dependent manner. EC supplemented with 23 or 28 mM vitamin E in the media for 22 h were maintained at normoxia (20% O<sub>2</sub>, 5% CO<sub>2</sub>, and balance N<sub>2</sub>) or exposed to hypoxic conditions (3% O<sub>2</sub>, 5% CO<sub>2</sub>, and balance N<sub>2</sub>) for 12 h, followed by reoxygenation (20% O<sub>2</sub>) for 30 min. Saphenous EC supplemented with 23 mM vitamin E produced less ( $p < 0.05$ ) H<sub>2</sub>O<sub>2</sub> than unsupplemented controls, both at normoxic condition (supplemented: 4.9 plus or minus 0.05 vs. control: 10.9 plus or minus 1.3 pmol/min/106 cells) and following hypoxia/reoxygenation (supplemented: 6.4 plus or minus 0.78 vs. control: 17.0 plus or minus 2.7 nmol/min/106 cells). In contrast, aortic EC, which were found to have higher superoxide dismutase and catalase activity than EC from saphenous vein, did not produce any detectable levels of H<sub>2</sub>O<sub>2</sub>. Following hypoxia/reoxygenation, the concentration of vitamin E in supplemented saphenous EC was 62% lower than cells maintained at normoxia (0.19 plus or minus 0.03 vs. 0.5 plus or minus 0.12 nmoles/106 cells.  $p < 0.001$ ); in aortic EC vitamin E content was reduced by 18% following reoxygenation (0.86 plus or minus 0.16 vs. 0.70 plus or minus 0.09 nmoles/106 cells,  $p < 0.05$ ). Therefore, enrichment of vitamin E in EC decreases H<sub>2</sub>O<sub>2</sub> production and thus may reduce the injury associated with ischemia-reperfusion events.

## **On the mechanism of the anticlotting action of vitamin E quinone**

Dowd P, Zheng ZB

Department of Chemistry, University of Pittsburgh, PA 15260, USA.

Proceedings of the National Academy of Sciences of the United States of America (USA), 1995, 92/18 (8171-8175)

Vitamin E in the reduced, alpha-tocopherol form shows very modest anticlotting activity. By contrast, vitamin E quinone is a potent anticoagulant. This observation may have significance for field trials in which vitamin E is observed to exhibit beneficial effects on ischemic heart disease and stroke. Vitamin E quinone is a potent inhibitor of the vitamin K- dependent carboxylase that controls blood clotting. A newly discovered mechanism for the inhibition requires attachment of the active site thiolgroups of the carboxylase to one or more methyl groups on vitamin E quinone. The results from a series of model reactions support this interpretation of the anticlotting activity associated with vitamin E.

## **Vitamin E may enhance the benefits of aspirin in preventing stroke**

Steiner M.

Memorial Hospital, Pawtucket, RI, United States

American Family Physician (USA), 1995, 51/8 (1977)

No abstract.

## **Antioxidant vitamins and disease - Risks of a suboptimal supply**

Ballmer PE, Reinhart WH, Gey KF

Departement Medizin, Inselspital, Universitat Bern.

Ther. Umsch. (Switzerland), 1994, 51/7 (467-474)

Reactive oxygen species (ROS) such as the superoxide (O<sub>2</sub><sup>-</sup>) and the hydroxyl radical (OH<sup>·</sup>) are aggressive chemical compounds that can induce tissue injury, e.g. by peroxidation of polyunsaturated fatty acids in cell membranes or directly by DNA damage. Many pathological conditions are in part caused by ROS. There are various biological defense systems directed towards radicals: specific enzymes, e.g. superoxide dismutase or glutathion peroxidase; nonessential antioxidants, e.g. the plasma proteins and uric acid; and the essential antioxidants, e.g. Vitamin-C, vitamin D and carotenoids. This review focuses on various clinical conditions where ROS are of major pathogenetic significance: ageing, cancer, stroke, hematologic disorders, adult respiratory distress syndrome (ARDS) and organ preservation in transplantation medicine. Moreover, the complementary system of the vitamins C and E in defense against ROS is shortly discussed and the need for further studies about the effects of antioxidant treatment, such as interventional studies, proposed. The chronic exposure of the organism to ROS is an important factor for tissue injury in the process of ageing. Lipofuscin is a typical product of lipid peroxidation and inversely correlates with longevity of an organism. The ingestion of higher doses of antioxidative vitamins was recently shown to be protective for the development of cataracts, a degenerative disorder of the eye. The impairment of the immune system in elderly people might be prevented by a higher intake of multivitamin supplements. Whether supplementation with antioxidative vitamins can extend the life span in humans, as was shown in experimental animals, remains unanswered. High intake of vegetables and fruits is associated with a significantly lower incidence of cancer, in particular of lung, but also of laryngeal, esophageal and colorectal cancer, which might be attributed to higher intake of antioxidant vitamins. As discussed in this issue of the journal by Gey et al., there is an inverse correlation between plasma status of antioxidant vitamins and coronary mortality due to prevention of atherosclerosis. There is also an inverse correlation between the risk of suffering from a fatal stroke and the plasma concentrations of antioxidant vitamins. Supplementation with vitamin E in some hematologic disorders such as beta-thalassemia and glucose-6-phosphatase-dehydrogenase deficiency showed an improvement of hemolysis. ARDS, a common cause of respiratory failure in severely ill patients, is a 'classical free radical disease'. Interventional studies with antioxidant vitamins for the treatment of ARDS are so far lacking. Reperfusion injury by a 'radical burst' may be a major cause for performance of organ transplants such as the kidney. The treatment with multivitamin preparations containing Vitamin-C and E was associated with better transplant performance in kidney transplants in a recent study. In conclusion, 'optimal' plasma concentrations of essential antioxidants are a primary aim in the prevention of disease such as ischemic heart disease, stroke and cancer. This is achieved by intake of higher doses of dietary antioxidants (as compared with RDAs) or, if necessary, by vitamin supplements.

## **Vitamin E consumption and the risk of coronary disease in women**

Stampfer MJ, Hennekens CH, Manson JE, Colditz GA, Rosner B, Willett WC  
Channing Laboratory, Boston, MA 02115.  
New Engl. J. Med. (USA), 1993, 328/20 (1444-1449)

Background. Interest in thocumented 552 cases of major coronary disease (437 nonfatal myocardial infarctions and 115 deaths due to coronary disease).

Results. As compared with women in the lowest fifth of the cohort with respect to vitamin E intake, those in the top fifth had a relative risk of major coronary disease of 0.66 (95 percent confidence interval, 0.50 to 0.87) after adjustment for age and smoking. Further adjustment for a variety of other coronary risk factors and nutrients, including other antioxidants, had little effect on the results. Most of the variability in intake and reduction in risk was attributable to vitamin E consumed as supplements. Women who took vitamin E supplements for short periods had little apparent benefit, but those who took them for more than two years had a relative risk of major coronary disease of 0.59 (95 percent confidence interval, 0.38 to 0.91) after adjustment for age, smoking status, risk factors for coronary disease, and use of other antioxidant nutrients (including multivitamins).

Conclusions. Although these prospective data do not prove a cause-and-effect relation, they suggest that among middle-aged women the use of vitamin E supplements is associated with a reduced risk of coronary heart disease. Randomized trials of vitamin E in the primary and secondary prevention of coronary disease are being conducted; public policy recommendations about the widespread use of vitamin E should await the results of these trials.

### **Increased risk of cardiovascular disease at suboptimal plasma concentrations of essential antioxidants: An epidemiological update with special attention to carotene and Vitamin-C**

Gey KF, Moser UK, Jordan P, Stahelin HB, Eichholzer M, Ludin E  
Vitamin Unit, University of Berne, Switzerland.  
Am. J. Clin. Nutr. (USA), 1993, 57/5 Suppl. (787S-797S)

For the prolongation of life expectancy and reduction of ischemic heart disease (IHD) dietary guidelines generally recommend lowering saturated mammalian fat with partial replacement by vegetable oils and increasing generously vegetables, legumes, and fruits, which provide more essential antioxidants. Plasma antioxidants as assayed in epidemiological studies of complementary type (ie the cross-cultural MONICA Vitamin Substudy reevaluation considering the 'Finland-Factor', the Edinburgh Angina-Control Study, and the Basel Prospective Study) consistently revealed an increased risk of IHD (and stroke) at low plasma concentrations of antioxidants, with the rank order as follows: lipid-standardized vitamin E >> carotene = Vitamin-C > vitamin A, independently of classical IHD risk factors. Decreasing IHD risk through nutrition may be possible when plasma concentrations have the following values: > 27.5-30.0 micromol vitamin E/L, 0.4-0.5 micromol carotene/L, 40-50 micromol Vitamin-C/L and 2.2-2.8 micromol vitamin A/L. Thus, previous prudent regimens may now be updated, aiming at an optimal status of all essential and synergistically linked antioxidants.

### **Lipid peroxide, phospholipids, glutathione levels and superoxide dismutase activity in rat brain after ischaemia: Effect of ginkgo biloba extract**

Seif-El-Nasr M, El-Fattah AA  
Department of Pharmacology, Cairo University, Egypt.  
Pharmacological Research (United Kingdom), 1995, 32/5 (273-278)

The influence of ginkgo biloba extract on the lipid peroxide product (malondialdehyde, MDA), glutathione (GSH) and phospholipids levels as well as superoxide dismutase (SOD, 1.15.1.1) and lactate dehydrogenase (LDH, 1.1.1.27) activities in rat brain after occlusion of common carotid arteries was investigated. Two experimental models were studied: 60 min ischaemia without reperfusion and 60 min ischaemia followed by 60 min reperfusion. Compared to sham-operated animals, ischaemia followed by reperfusion increased cytosolic LDH activity and mitochondrial lipid peroxide content and decreased the superoxide dismutase activity and mitochondrial total phospholipids level. Preischaemic administration of ginkgo biloba extract (150 mg kg<sup>-1</sup>, p.o.) could normalize the SOD activity of the rat brain. The extract was also able to reduce the lipid peroxide and phospholipids contents of the mitochondrial rat brain. These effects could be explained on the basis of the antioxidant property of ginkgo biloba extract and suggests its beneficial role in the protection against post-ischaemic injury.

### **Protection of hypoxia-induced ATP decrease in endothelial cells by ginkgo biloba extract and bilobalide**

Janssens D, Michiels C, Delaive E, Eliaers F, Drieu K, Remacle J  
Laboratoire de Biochimie Cellulaire, Facultes Universitaires Notre Dame de la Paix, Namur, Belgium.  
Biochemical Pharmacology (United Kingdom), 1995, 50/7 (991-999)

Due to their localization at the interface between blood and tissue, endothelial cells are the first target of any change occurring within the blood, and alterations of their functions can seriously impair organs. During hypoxia, which mimics in vivo ischemia, a cascade of events occurs in the endothelial cells, starting with a decrease in ATP content and leading to their activation and release of inflammatory mediators. EGb 761 and one of its constituents, bilobalide, were shown to inhibit the hypoxia-induced decrease in ATP content in endothelial cells in vitro. Under these conditions, glycolysis was activated, as evidenced by increased glucose transport, as well as increased lactate production. Bilobalide was found to increase glucose transport under normoxic but not hypoxic conditions. In addition, EGb and bilobalide prevented the increase in total lactate production observed after 60 min of hypoxia. However, after 120 min of hypoxia, the total lactate production was similar under normoxic and hypoxic conditions, and both compounds increased this production. These results indicate that glycolysis slowed down between the 60th and 120th minute of hypoxia, while EGb and bilobalide delayed the onset of glycolysis activation. In another experimental model, both compounds were shown to increase the respiratory control ratio of mitochondria isolated from liver of rats treated orally. Since ischemia is known to uncouple mitochondria, the protection of ATP content and the delay in glycolysis activation observed during hypoxia in the presence of EGb 761 or bilobalide is best explained by a protection of mitochondrial respiratory activity, at least during the first 60 min of hypoxia incubation. Both products retain the ability to form ATP, thereby reducing the cell's need to induce glycolysis, probably by preserving ATP regeneration by mitochondria as long as oxygen is available.

### **Lipid peroxidation in experimental spinal cord injury. Comparison of treatment with Ginkgo biloba, TRH and methylprednisolone**

Koc RK, Akdemir H, Kurtsoy A, Pasaoglu H, Kavuncu I, Pasaoglu A, Karakucuk I  
Department of Neurosurgery, Erciyes University, School of Medicine, Kayseri, Turkey.  
Research in Experimental Medicine (Germany), 1995, 195/2 (117-123)

Ischaemia-induced lipid peroxidation is one of the most important factors producing tissue damage in spinal cord injury. In our study, the protective effects of Ginkgo biloba, thyroid releasing hormone (TRH) and methylprednisolone (MP) on compression injury of the rat spinal cord were investigated. For this study 45 rats in four groups, including control, MP, TRH and Ginkgo biloba, were used to determine the formation of malondialdehyde (MDA). All the animals were made paraplegic by the application clip method of Rivlin and Tator. Rats were divided randomly and blindly to one of four treatment groups (ten animals in each). MP and Ginkgo biloba treatments significantly decreased MDA levels ( $F=54.138$ ,  $P<0.01$ ). These results suggest that MP and Ginkgo biloba may have a protective effect against ischaemic spinal cord injury by the antioxidant effect.

### **Effects of natural antioxidant Ginkgo biloba extract (EGb 761) on myocardial ischemia-reperfusion injury**

Haramaki N, Aggarwal S, Kawabata T, Droy-Lefaix MT, Packer L  
Department of Molecular and Cell Biology, University of California, Berkeley 94720.  
Free Radic. Biol. Med. (USA), 1994, 16/6 (789-794)

Recently, it was reported that Ginkgo biloba extract (EGb 761), which is known to have antioxidant properties, also has antiarrhythmic effects on cardiac reperfusion-induced arrhythmias. In the present study, effects of EGb 761 on cardiac ischemia-reperfusion injury were investigated from the point of view of recovery of mechanical function as well as the endogenous antioxidant status of ascorbate. Isolated rat hearts were perfused using the Langendorff technique, and 40 min of global ischemia were followed by 20 min of reperfusion. EGb 761 improved cardiac mechanical recovery and suppressed the leakage of lactate dehydrogenase (LDH) during reperfusion. Furthermore, EGb 761 diminished the decrease of myocardial ascorbate content after 40 min of ischemia and 20 min of reperfusion. Interestingly, EGb 761 also suppressed the increase of dehydroascorbate. These results indicate that EGb 761 protects against cardiac ischemia-reperfusion injury and suggest that the protective effects of EGb 761 depend on its antioxidant properties.

### **Experimental model of cerebral ischemia. Preventive activity of Ginkgo biloba extract**

Rapin JR, Le Poncin-Lafitte M  
Sem. Hop. (France), 1979, 55/43-44 (2047-2050)

Unilateral embolization of the brain was performed in rats by intracarotid injection of 4000 radioactive microspheres (50  $\mu$ m). Local blood flow in hippocampus, striatum, hypothalamus and remainder of the brain were determined using the iodoantipyrine technique. Embolization resulted in a decrease in blood flow and modification of the distribution of microflow. Furthermore, embolization produces changes in energy metabolism: particularly a fall in ATP and glucose levels and an increase in lactate level. Subsequently, severe vasogenic edema development. There was a correlation between the number of microspheres injected and the amount of edema. Pretreatment using an extract of Ginkgo biloba leaves partially suppressed the effect of embolization. An improvement of the flow in the ischemic areas associated with an improvement of the energy metabolism explain the decrease of the edema.

**On brain protection of co-dergocrine mesylate (Hydergine (R)) against hypoxic hypoxidosis of different severity: Double-blind placebo-controlled quantitative EEG and psychometric studies**

Saletu B, Grunberger J, Anderer R

Division of Pharmacopsychiatry, Psychiatric University Clinic of Vienna, Austria.

Int. J. Clin. Pharmacol. Ther. Toxicol. (Germany, Federal Republic of), 1990, 28/12 (510-524)

Utilizing quantitative EEG and psychometric methods we investigated in two subsequent double-blind, placebo-controlled trials the following questions:

- 1) Does co-dergocrine mesylate (CDM) protect against cerebral hypoxic hypoxidosis as objectivated by neurophysiological and behavioral measures in man?
- 2) Does CDM offer protection equally both against moderate and marked hypoxia induced experimentally by inhalation of a gas mixture of 9.8% and 8.6% O<sub>2</sub> (equivalent to 6000 m and 7000 m altitude, respectively)?
- 3) Are brain-protective effects of CDM improving by drug administration over a longer period of time (2 weeks)?

In the first study, hypoxic hypoxidosis was induced by a fixed gas combination of 9.8% oxygen and 90.2% N<sub>2</sub> (equivalent to 6000 m altitude), which was inhaled for 23 min under normobaric conditions by 15 healthy volunteers. They received randomized, after an adaptation session, placebo and 5 mg CDM. Blood gases, quantitative EEG, and psychometric measures were obtained under normoxic (21% O<sub>2</sub>) and hypoxic (9.8% O<sub>2</sub>) conditions before as well as 2, 4, 6 and 8 h after oral drug administration. Blood gas analysis demonstrated under hypoxia a drop in PO<sub>2</sub> from 91 to 37 mmHg and in PCO<sub>2</sub> from 38 to 33 mmHg, while pH increased from 7.41 to 7.47. Computer-assisted spectral analysis of the EEG showed an increase of delta/theta, decrease of alpha, and an increase of superimposed fast beta activity indicative of deterioration in vigilance. The latter was documented at the behavioral level by deterioration of intellectual and mnesic functions, psychomotor activity, performance in a reaction time task, mood, and wakefulness. CDM attenuated significantly this brain dysfunction, as it attenuated delta/theta and increased alpha-adjacent beta activity. Psychometric performance based on all 11 variables deteriorated under hypoxia by 49% after placebo, while after 5 mg CDM only by 26%. However, in a subsequent double-blind placebo-controlled trial in 12 healthy young volunteers, further augmentation of hypoxia induced by inhalation of a gas combination of 8.6% O<sub>2</sub> and 91.4% N<sub>2</sub> (equivalent to 7000 m altitude) leading to a drop of PO<sub>2</sub> and PCO<sub>2</sub> to 32 and 32 mmHg, respectively and an increase of pH to 7.46 resulted in a loss of brain protection, even when CDM was given over 2 weeks daily. Our findings suggest that treatment of organic brain syndromes with nootropic/antihypoxidotics should be initiated in an early rather than a late stage.

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## STROKE (THROMBOTIC)

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**[Pharmacodynamics of the cerebral circulation. Results of a study on the action of 10 drugs on cerebral blood flow and energy metabolism in cerebrovascular patients]**

Marc-Vergnes JP; Bes A; Charlet JP; Delpla M; Richardot JP; Geraud J  
Pathol Biol (Paris) 1974 Nov;22(9):815-25

The authors studied the action of 10 drugs on cerebral blood flow and metabolism in patients with cerebrovascular insufficiency. The difficulties of this type of study are due to the techniques of measurement of cerebral blood flow which are traumatic, long and relatively inaccurate. Their traumatic character, which is mainly marked in the case of xenon <sup>133</sup>Xe clearance, limits their field of application and renders difficult experimental plans. The length of the examination restricts the possibilities offered during the same session. Finally, owing to the relatively inaccurate measurements, only important changes can be noted. However, during 2 successive series of measurements, carried out by 2 different methods of measurement of cerebral blood flow, only preparations containing hydergine induced a statistically significant increase in cerebral blood flow and oxygen consumption in the brain. This finding, which proves that a drug may modify the parameters, encourages better integration of pharmacodynamic tests in the physiopathological investigations carried out during the course of a disease.

**Effects of ionic and nonionic contrast media on clot structure, platelet function and thrombolysis mediated by tissue plasminogen activator in plasma clots**

Carr ME Jr, Carr SL, Merten SR  
Department of Medicine, Medical College of Virginia, Richmond, USA.  
Haemostasis (Switzerland), 1995, 25/4 (172-181)

Various radiographic contrast agents have anticoagulant or prothrombotic properties. Ionic agents are reported to have greater antithrombotic potential while nonionic agents are considered more thrombogenic. Some agents alter fibrin structure and bind to platelets in purified systems. This study compared the effects of iohexol, a nonionic agent, and iothalamate, an ionic agent, on fibrin assembly, clot structure, platelet function and clot dissolution in plasma. Plasma gels containing increasing concentrations

of iohalamate were composed of thinner fibers with decreased fiber mass/length ratios (micro) and reduced gel turbidity. Such clots were more rigid and more resistant to fibrinolysis induced by tissue plasminogen activator (tPA). Gel elastic modulus increased from 10,000 to 27,000 dyn/cm<sup>2</sup> as iohalamate concentration increased from 0 to 20 mM. 50% lysis time increased from 800 to 1,250 s with the addition of 10 mM iohalamate. At 20 mM, iohalamate had no effect on ADP-induced platelet aggregation but prolonged the lag phase seen with collagen-induced aggregation. Platelet force development increased from 15,300 to 20,400 dyn with 20 mM iohalamate. The effects of iohexol were similar. Gel optical density dropped from 0.50 to 0.32, micro fell from 3.3 to 2.2 x 10<sup>13</sup> D/cm, and elastic modulus rose from 11,000 to 24,000 dyn/cm<sup>2</sup> as iohexol concentration was increased from 0 to 20 mM. Clots formed in the presence of 60 mM iohexol and tPA did not dissolve in 72 h while control clot 50% lysis time was 450 s. At concentrations greater than or equal to 40 mM, iohexol completely blocked collagen-induced platelet aggregation. Platelet force development increased from 7,660 to 19,600 with 40 mM iohexol. Contrast media possess profound fibrin-altering activities in plasma. Fibrin formed in the presence of some agents may be significantly more resistant to fibrinolysis.

### **Thrombolytic therapy: Recent advances. Treatment of myocardial infarction**

Appl. Cardiopulm. Pathophysiol. (Netherlands), 1991/92, 4/3 (193-204)

The objectives of thrombolytic therapy in acute myocardial infarction are to restore coronary artery patency, salvage myocardium, reduce infarct size, and facilitate coronary artery repair. Urokinase and streptokinase are the two most frequently used thrombolytic agents. Both dissolve thrombi by converting circulating plasminogen, an inert precursor, into plasmin. One possible advantage of urokinase and streptokinase over new 'clot-specific' agents, recombinant tissue plasminogen activator (rt-PA) anisoylated SK-plasminogen activator complex (APSAC) and antibody directed UK, SK and rt-PA, is that the former have pronounced systemic fibrinolytic effects. This reduces blood viscosity and may prevent other thrombi from forming. Angiography is the most objective technique for assessing reestablished arterial patency, but being invasive, it presents disadvantages. Noninvasive criteria for coronary reperfusion include lowering of elevated ST-segments, shifting creatine kinase isoenzyme MB curves, and the appearance of reperfusion arrhythmias. Techniques for assessing myocardial salvage include thallium uptake, assessment of wall motion and myocardial thickening, ejection fraction, and positron emission tomography to assess infarct size. The role and appropriate timing of coronary artery repair after thrombolytic therapy are being studied intensely. There is no question that thrombolytic agents have made a significant beneficial impact and advance in the treatment of myocardial infarction. Considerable information has indicated that physicians must be educated in the details of use of thrombolytic agents and they must intensely educate their patients on the need to make themselves available to this treatment immediately when suggested by the symptoms and signs of this disease process.

### **Selective decrease in lysis of old thrombi after rapid administration of tissue-type plasminogen activator**

Kanamasa K, Watanabe I, Cercek B, Yano J, Fishbein MC, Ganz W  
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J. Am. Coll. Cardiol. (USA), 1989, 14/5 (1359-1364)

The safety of thrombolytic therapy of acute myocardial infarction could be improved if a method were developed to dissolve fresh occlusive coronary thrombus without simultaneously dissolving hemostatic thrombi outside the coronary arteries. This study is based on the assumption that, in a patient with evolving acute myocardial infarction, hemostatic thrombi are likely to be older than the thrombus responsible for occlusion of the coronary artery. It explored whether the relative rates of lysis of fresh and old thrombi could be influenced by the rapidity of recombinant tissue-type plasminogen activator (rt-PA) administration. In each of 17 dogs, two 1 h and two 24 h old thrombi were produced by inserting copper coils into both jugular and both femoral veins. After 24 h and 1 h, respectively, the coils with the thrombi were removed, weighed and inserted into the adjacent carotid and femoral arteries. A 1 mg/kg body weight dose of rt-PA was given either over 180 or over 30 min. The coils were removed and weights of the residual thrombi determined at the end of the 180 min infusion (Group I), at the end of the 30 min infusion (Group IIA) and 45 min after the 30 min infusion (Group IIB). The 24 h old thrombi were lysed significantly less than the 1 h old thrombi in all three experimental groups: 53.9 plus or minus 4.8% (mean plus or minus SE) versus 86.1 plus or minus 2.5% in Group I ( $p < 0.001$ ), 16.6 plus or minus 3.5% versus 65.2 plus or minus 6.0% in Group IIA ( $p < 0.001$ ) and 21.6 plus or minus 5.4% versus 91.7 plus or minus 1.7% in Group IIB ( $p < 0.001$ ). The 24 h old thrombi were also lysed significantly less by the 30 min infusion than by the 180 min infusion ( $p < 0.001$  for both). The ratio of lysis of 1 and 24 h old thrombi was markedly higher in Groups IIA (7.95 plus or minus 2.16) and IIB (6.52 plus or minus 1.50) than in Group I (1.71 plus or minus 0.17) ( $p < 0.01$  for both). These findings suggest that rt-PA administered rapidly over a shorter period is less likely to lyse older thrombus, whereas the effect on fresh thrombus is preserved and probably enhanced. Clinical studies are needed to confirm the conclusions of this experimental study.

### **Antioxidant Curcuma extracts decrease the blood lipid peroxide levels of human subjects**

Ramirez-Bosa A, Solfer A, Gutierrez M, Alvarez J, Almagro E  
Age (USA), 1995, 18/4 (167-169)

Extracts of the rhizome of *Curcuma longa* are widely used as food additives in India and other Asiatic and Central American countries. Moreover, it has been recently shown that these extracts ('turmeric'), as well as 'curcumin' and related phenolic compounds isolated from *Curcuma*, have a powerful lipid antioxidant action, when tested in *in vitro* systems. This justifies the present attempt to find out whether hydroalcoholic extracts of *Curcuma longa* also exert an antioxidant effect in human subjects. Our data show that a 45-day intake (by healthy individuals ranging in age from 27 to 67 years) of *Curcuma* hydroalcoholic extract (at a daily dose equivalent to 20 mg of curcumin) results in a significant decrease in the levels of serum lipid peroxides. These peroxides probably play an important pathogenic role in normal senescence and age-related diseases such as atherosclerosis. Therefore, hydroalcoholic extracts of *Curcuma longa* (that have very low toxicity and have been cleared as food additives in the above countries) may find use in future preventive geriatrics after further clinical studies.

### **Inhibition of tumor necrosis factor by curcumin, a phytochemical**

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Biochem Pharmacol 1995 May 26;49(11):1551-6

Curcumin, contained in the rhizome of the plant *Curcuma longa* Linn, is a naturally occurring phytochemical that has been used widely in India and Indonesia for the treatment of inflammation. The pleiotropic cytokine tumor necrosis factor- $\alpha$  (TNF) induces the production of interleukin-1 $\beta$  (IL-1), and, together, they play significant roles in many acute and chronic inflammatory diseases. They have been implicated in the pathogenesis of intracellular parasitic infections, atherosclerosis, AIDS and autoimmune disorders. This report shows that, *in vitro*, curcumin, at 5  $\mu$ M, inhibited lipopolysaccharide (LPS)-induced production of TNF and IL-1 by a human monocytic macrophage cell line, Mono Mac 6. In addition, it demonstrates that curcumin, at the corresponding concentration, inhibited LPS-induced activation of nuclear factor  $\kappa$ B and reduced the biological activity of TNF in L929 fibroblast lytic assay.

### **Inhibitory effect of curcumin, an anti-inflammatory agent, on vascular smooth muscle cell proliferation**

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Eur J Pharmacol 1992 Oct 20;221(2-3):381-4

The effects of curcumin, an anti-inflammatory agent from *Curcuma longa*, on the proliferation of blood mononuclear cells and vascular smooth muscle cells were studied. Proliferative responses were determined from the uptake of tritiated thymidine. In human peripheral blood mononuclear cells, curcumin dose dependently inhibited the responses to phytohemagglutinin and mixed lymphocyte reaction at the dose ranges of  $10^{-6}$  to  $3 \times 10^{-5}$  and  $3 \times 10^{-6}$  to  $3 \times 10^{-5}$  M, respectively. Curcumin ( $10^{-6}$  to  $10^{-4}$  M) dose dependently inhibited the proliferation of rabbit vascular smooth muscle cells stimulated by fetal calf serum. Curcumin had a greater inhibitory effect on platelet-derived growth factor-stimulated proliferation than on serum-stimulated proliferation. Cinnamic acid, coumaric acid and ferulic acid were much less effective than curcumin as inhibitors of serum-induced smooth muscle cell proliferation, suggesting that the cinnamic acid and ferulic acid moieties alone are not sufficient for activity, and that the characteristics of the diferuloylmethane molecule itself are necessary for activity. Curcumin may be useful as a new template for the development of better remedies for the prevention of the pathological changes of atherosclerosis and restenosis.

### **Change of fatty acid composition, platelet aggregability and RBC function in elderly subjects with administration of low dose fish oil concentrate and comparison with those in younger subjects**

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Nippon Ronen Igakkai Zasshi 1994 Aug;31(8):596-603

Anti-thrombotic and anti-atherogenic effects of eicosapentaenoic acid (EPA) through the modulation of various cell functions related to thrombogenesis have been reported recently. We previously reported that the administration of EPA at low doses could more effectively elevate the plasma EPA concentration in elderly subjects than in younger ones. Magnetic resonance imaging

examination of the brain often reveals lacunar lesions in elderly subjects without any signs or symptoms of cerebrovascular diseases. In this study we clarified the effect of administration of low doses of fish oil concentrate on platelet and RBC function in elderly subjects, compared with younger subjects. Thirty-six elderly subjects (mean age 78) without any signs or symptoms of cerebrovascular diseases, all receiving the same diet in the same lodging house for the aged, were divided into 3 groups. Different amounts of fish oil concentrate (0.25-0.5 g/day of EPA) were administered to the 3 groups, daily for more than 1 month. Changes of plasma fatty acid composition, platelet aggregability, whole blood viscosity and RBC deformability was examined before and after EPA administration. One month after EPA treatment, the plasma EPA content had increased dose dependently, with suppression of platelet aggregation and improvement of RBC function. In younger subjects receiving the same amount of EPA, the elevation of plasma EPA was less than that observed in the elderly. In summary, low dose EPA administration can improve the function of platelet and RBC to an anti-thrombotic state and would be useful to prevent the occurrence of cerebrovascular diseases in elderly subjects without any side effects.

### **Premature Carotid Atherosclerosis: Does It Occur in Both Familial Hypercholesterolemia and Homocystinuria? Ultrasound Assessment of Arterial Intima-Media Thickness and Blood Flow Velocity"**

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Stroke, May 1994;25(5):943-950

This study evaluated 12 patients with homocystinuria due to cystathionine B-synthase deficiency, 10 patients with homozygous familial hypercholesterolemia and 11 healthy controls for the possibility that different patterns of carotid wall damage and cerebral blood flow hemodynamics were present. B-mode ultrasound mean maximum intima-media thickness was 1.4 mm in patients with familial hypercholesterolemia, 0.6 mm in patients with homocystinuria and 6 mm in control subjects. The difference between hypercholesterolemic and homocystinuric patients or control subjects was statistically significant. Diastolic blood flow velocities were significantly reduced in the middle cerebral arteries of hypercholesterolemic patients compared with homocystinuric patients or control subjects, whereas systolic or mean velocities did not differ. The pulsatility index, a possible indicator of vascular resistance in cerebral circulation, was significantly higher in hypercholesterolemic patients compared with the homocystinuric patients or healthy control subjects. There was a direct relationship demonstrated between the pulsatility index of the middle cerebral artery and the mean maximum intima-media thickness of the carotid arteries on the same side. The authors conclude familial hypercholesterolemia is responsible for diffuse and focal thickening of the coronary arteries and possibly for the hyperlipidemic endothelial dysfunction seen in the small resistance arteries leading to a disturbed cerebral blood flow. Patients with homocystinuria seldom have plaques in their carotid arteries. In fact, their arteries are similar to healthy controls with regards to intima-media thickness and blood flow velocity in the middle cerebral artery. It is not likely that typical atherosclerotic lesions precede thrombotic events in homocystinuria. It may be that arterial dilations caused by medial damage lead to thrombosis in homocystinuric patients. The mechanism underlying the thrombotic events seen in early-treated vitamin B6 responsive homocystinuric patients is not known.

### **Fibrinogen, Arterial Risk Factor in Clinical Practice**

Potron G, Nguyen P, Pignon B  
Clinical Hemorrhology, 1994;14(6):739-767

Ten large studies have confirmed that fibrinogen is a risk factor of equal or higher value than total cholesterol. Fibrinogen is an independent risk factor and is an independent and prognostic risk factor for coronary artery disease. After a stroke an elevated fibrinogen is an index of the severity of the condition. In peripheral arterial disease it is an indicator of the risk to reocclusion after surgery. Fibrinogen's role in arterial occlusion include the composition of the atheroma plaque, thrombi formation, endothelial injury and hyperviscosity. Fibrinogen can be increased by inflammation, aging and smoking. Drugs that may reduce fibrinogen include fibrates and the platelet inhibitor ticlopidin. Physical exercise if sustained can reduce fibrinogen.

### **Fibrinogen and Cardiovascular Disorders**

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Quarterly Journal of Medicine, 1995;88:155-165

This is an extensive review article on the role of fibrinogen and cardiovascular disease. Fibrinogen is involved in blood coagulation

and is an important determinant of blood viscosity and blood flow. Elevated plasma fibrinogen levels have been epidemiologically shown to increase the risk for cardiovascular disorders. These include ischemic heart disease, stroke and other thromboembolic events. Increased plasma fibrinogen may promote a prothrombotic or hypercoagulable state, and may, in part, explain the risk of stroke and thromboembolism in conditions such as atrial fibrillation and cardiac dysfunction. Human fibrinogen is a large glycoprotein (340,000 Da) composed of 3 pairs of nonidentical polypeptide chains (A alpha, B beta and gamma) joined together by disulphide bonds. Fibrinogen is an important determinant of both rheological characteristics of blood flow and of platelet aggregability. Fibrinogen is an essential component of the blood coagulation system, being the precursor of fibrin. Usual plasma levels are between 1.5 and 4.5 g/l, a concentration far greater than the minimum concentration needed of 0.5 to 1 g/l for haemostasis. In 9 out of 10 studies, plasma fibrinogen levels correlated significantly with the degree of coronary artery disease. A positive correlation between plasma fibrinogen and fibrin D-dimer has been seen in patients with atrial fibrillation. Intermediate levels of plasma fibrinogen have also been found in patients with paroxysmal atrial fibrillation. Psychological and mental stress can increase plasma fibrinogen levels. Fibrinogen levels are significantly associated with cerebrovascular disease. Plasma fibrinogen concentrations have been shown to be an important independent predictor of coronary death in patients with intermittent claudication. In patients with systemic hypertension, fibrinogen concentrations and plasma viscosity are independent predictors of blood pressure. In diabetic patients, a significant positive correlation has been found between plasma fibrinogen and fasting glucose levels, serum cholesterol levels, glycosylated hemoglobin and urinary albumin excretion rates. In individuals who use oral contraceptives, an increased risk of thrombotic events measured by elevated platelet aggregation and plasma fibrinogen levels has been discovered. There appears to be a hormonal influence on fibrinogen levels. Smoking has a dose- effect relationship on plasma fibrinogen levels. In obese patients with a body mass index of more than 30, plasma viscosity and fibrinogen levels are significantly increased. Strenuous exercise is associated with lower fibrinogen and cholesterol concentrations. Increased alcohol consumption may have a small but significant effect on decreasing plasma fibrinogen levels. The role of social class and psychosocial factors in determining plasma fibrinogen levels is controversial. Plasma fibrinogen levels are increased in patients with hyperlipidaemia. Dental disease is associated with myocardial infarction, and increased fibrinogen and white blood cell counts may partly explain this. The genetic influence on plasma fibrinogen formation, and genetic heritability, may account for 51% of the variance of plasma fibrinogen levels. There is a wide range of reference values for plasma fibrinogen with a mean "normal" value between 2.3 and 3.1 g/l in different population studies. Elevated plasma fibrinogen levels are consistently associated with various cardiovascular disorders. Because the process of atherogenesis has similarities to inflammatory diseases, the elevation of plasma fibrinogen levels may reflect the severity of the vascular disorder as a secondary phenomenon rather than act as a true prognostic factor. The strong hereditary determination of fibrinogen makes it less likely that raised fibrinogen levels are simply a secondary response to cardiovascular disorders. Raised plasma fibrinogen levels are known to precede in cardiovascular disorders. Raised plasma fibrinogen levels are likely to reflect a pre-existing prothrombotic, or hypercoagulable, state. Acts to lower fibrinogen levels include ceasing smoking and increasing exercise. Drugs that may lower fibrinogen include ticlopidine, stanzolol, oxyphenyflline, calcium dobesilate, propranolol, nislodipine and the fibrates. These drugs have other pharmacologic effects other than lowering fibrinogen concentrations and are not practical therapeutic options. There is controversy with regards to diet lowering plasma fibrinogen levels. Fish oil supplementation may result in the reduction in plasma fibrinogen levels. Moderate alcohol consumption, increased garlic, regular exercise, weight loss and better diabetic control are also favorable to lowering fibrinogen levels.

## **Can Lowering Homocysteine Levels Reduce Cardiovascular Risk?**

Stampfer MJ, Malinow MR

The New England Journal of Medicine, February 2, 1995;332(5):328-329.

Consistent findings have emerged from more than 20 case-control and cross-sectional studies of over 2,000 subjects indicating that patients with stroke and other cardiovascular diseases tend to have higher levels of homocysteine than those without the disease even though most have values within the normal range. In the Physician's Health Study, the 271 men who later had myocardial infarctions had significantly higher mean base-line levels of homocysteine than matched controls who were free of infarction. Men whose homocysteine levels were in the highest 5 percent had three times the risk of myocardial infarction than those with lower levels, even after adjustment for coronary risk factors. The prevalence of carotid-artery stenosis has been shown to be related to increasing plasma levels of homocysteine. One hypothesis regarding homocysteine's effects on cardiovascular disease is that damage stems from a toxic effect by homocysteine on vascular endothelium, which impairs the production of endothelium-derived relaxing factor. Homocysteine may stimulate the proliferation of smooth muscle cells, which is part of atherogenesis. Homocysteine can also act as a thrombogenic agent. The most dramatic elevations of homocysteine, which lead to life threatening vascular abnormalities at a young age, are due to an enzyme defect. Inadequate folic acid intake is the main determinant of homocysteine-related increase in carotid-artery thickening. Folic acid, vitamins B6 and B12, all play an important role in homocysteine metabolism. Homocysteine levels reach a stable low level only when folic acid intakes of approximately 400 ug per day or more are sustained. Folic acid supplements in the range of 1 to 2 mg per day are generally innocuous, and usually are sufficient to reduce or normalize high homocysteine levels, even if the elevation is not due to inadequate folic acid supplementation. When folic acid consumption is high the minor and common genetic variances have no clinical significance. But when folic consumption is marginal the risk may be elevated. In the Physician's Health Study, 5 percent of the controls had plasma homocysteine levels above 15.8 umol/L, the level which is associated with a three-fold increased risk of myocardial infarction. In the older and less highly selected population of the Framingham Heart Study, 21 percent had high levels of

homocysteine. The author notes, "Because the weight of evidence is substantial and the intervention appears to be benign, it may be possible to make broad preliminary recommendations based on trials of secondary prevention or disease progression rather than wait for large, expensive and prolonged trials of primary prevention. In the meantime, it will be prudent to ensure adequate dietary intake of folate".

### **The Lipoprotein(a). Significance and Relation to Atherosclerosis**

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ACTA Clinica Belgica, 1991;46(6):371-383

Lipoprotein(a) is very similar to low density lipoprotein, but possesses a unique protein moiety called apolipoprotein (A). The plasma concentration of lipoprotein(a) is mainly under genetic control. Nicotinic acid (vitamin B3) and neomycin are able to reduce its concentration. Epidemiologic studies suggest that high levels of lipoprotein(a), greater than 30 mg per dl, are an independent risk factor for atherosclerosis of the coronary and carotid arteries. The risk is highest in those with hypercholesterolemia. High lipoprotein(a) levels could also favor thrombosis. Reducing hypercholesterolemia is important when lipoprotein(a) levels are greater than 30 mg per dl.

### **Diminished production of malondialdehyde after carotid artery surgery as a result of vitamin administration**

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Medical Science Research (United Kingdom), 1996, 24/11 (777-780)

The objective of this study was to establish the antioxidative effect of the vitamins E, C and retinyl palmitate (vitamin A), contained in a multivitamin solution, in carotid artery revascularisation surgery. 57 patients, 67.84 plus or minus 5.72 years of age, 39 men and 18 women, were divided into a control group (27 subjects) and a group with 30 subjects (mean age 68.46 plus or minus 5.09 years) who received the vitamin treatment immediately before the start of reperfusion of the brain. The control group (mean age 67.14 plus or minus 6.37 years) received physiological sodium chloride as placebo. All of the patients suffered from ischaemic cerebrovascular insufficiency manifested as TIA (transitory ischaemic attack) due to haemodynamically significant stenosis of the extracranial part of the ICA (internal carotid artery). Oxidative burst was measured by malondialdehyde (MDA) - thiobarbituric acid reactive substances (TBARS) perioperatively before and 0.5, 1, 2 and 3 h after revascularisation. In the control group MDA-TBARS significantly increased from 0.91 plus or minus 0.49 to 1.15 plus or minus 0.41 nmol mL<sup>-1</sup> ( $p < 0.003$ ) 1 h after reperfusion onset and returned to baseline after 2-3 h. In the vitamin-treated group MDA-TBARS steadily decreased during the reperfusion period (1.11 plus or minus 0.39, 0.91 plus or minus 0.42, 0.81 plus or minus 0.29, 0.78 plus or minus 0.39, 0.72 plus or minus 0.24 nmol mL<sup>-1</sup>). The significant difference in MDA-TBARS between control and treatment groups, 1 h after the start at reperfusion was 1.15 plus or minus 0.41 vs 0.81 plus or minus 0.29 nmol mL<sup>-1</sup>; ( $p < 0.001$ ). As an indirect parameter of reperfusion injury 13% (4/30 patients) of the patients in the treatment group suffered... The perioperative use of antihypertensive drugs was 20% (6/30) in the treatment group, as compared to 78% (21/27) in the control group. These results suggests that vitamin treatment prior to reperfusion might be of beneficial effect, alleviating lipid peroxidation and leading to a better clinical course as regards the central nervous system.

### **Spermine partially normalizes in vivo antioxidant defense potential in certain brain regions in transiently hypoperfused rat brain**

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Neurochemical Research (USA), 1996, 21/12 (1497-1503)

Activities of the antioxidant enzymes such as superoxide dismutase (Cu,Zn-SOD), glutathione peroxidase (GSH-Px), glutathione reductase (GSSG-R) as well as the level of reduced glutathione and the concentration of thiobarbituric acid-reactive substance (TBARS) in brain regions in transiently hypoperfused rat brain with or without intravenous infusion of spermine were evaluated. Cerebral hypoperfusion was induced by temporary occlusion of common carotid arteries for 30 min and subsequently, by reperfusion for 60 min. Infusion of spermine reversed the decrease in SOD activity in the cerebral cortex, striatum, hippocampus, hypothalamus and midbrain, and amounted to 50.1 U, 61.5 U, 50.3 U, 30.0 U, 38.0 U, respectively, while GSH-Px restored to normal values only in the cerebral cortex and striatum and amounttter use of spermine no changes in GSSG-R were seen in the

hypothalamus and midbrain. The activity of GSSG-R was in accordance with the control for the striatum and amounted to 39.0 IU after using spermine, GSH content returned to normal values in the striatum and midbrain after i.v. use of spermine and amounted to 210 and 240 nmol/g of wet tissue, respectively. In addition, the production of TBARS dropped markedly ( $P < 0.05$ ) in the hippocampus and midbrain and amounted to 100 and 105 micromol/g of wet tissue, respectively. Partially beneficial effect of spermine could result from the inhibition of free radical generation and capability of chelate formation with iron ions.

### **Positron-labeled antioxidant 6-deoxy-6-(18F)fluoro-L-ascorbic acid: Increased uptake in transient global ischemic rat brain**

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Nuclear Medicine and Biology (USA), 1996, 23/4 (479-486)

The in vivo uptake and distribution of 6-deoxy-6-(18F)fluoro-L-ascorbic acid (18F-DFA) were investigated in rat brains following postischemic reperfusion. Global cerebral ischemia was induced in male Wistar rats for 20 min by occlusion of four major arteries. Two time points were chosen for 18F-DFA injection to rats subjected to cerebral ischemia, at the start of recirculation and 5 days following recirculation. The rats were then killed at 2 h after tail-vein administration of 18F-DFA and tissue radioactivity concentration was determined. Increased uptake of radioactivity in particular brain regions, including the cerebral cortex, hypothalamus, and amygdala following injection of 18F-DFA, compared to the sham operated control, was observed 5 days after reperfusion. Similar results were also obtained in in vitro experiments using brain slices. Abnormal  $^{45}\text{Ca}$ , a marker of regional postischemic injury, was observed in these brain regions in tissue dissection experiments. Furthermore, metabolite analysis of nonradioactive DFA using  $^{19}\text{F}$ -NMR showed that DFA remained intact in the postischemic reperfusion brain. The present results indicate that 18F-DFA increasingly accumulates in damaged regions of postischemic reperfusion brain.

### **Stroke is an emergency**

[No authors listed.]

Disease-a-Month (USA), 1996, 42/4 (202-264)

Stroke is an emergency. Ischemic stroke is similar to myocardial infarction in that the pathogenesis is loss of blood supply to the tissue, which can result in irreversible damage if blood flow is not restored quickly. Public education is needed to emphasize the warning signs of stroke. Patients should seek medical help immediately, using emergency transport systems. Therapy geared toward minimizing the damage from an acute stroke should be started without delay in the emergency room. This includes measures to protect brain tissue, support perfusion pressure, and minimize cerebral edema. Strategies for improving recovery should also begin immediately. All major medical centers need stroke teams and stroke units. Stroke prevention should be given high priority as a public health strategy. Risk factor management should be part of general health care and should begin in childhood, with emphasis on nutrition, exercise, weight control, and avoidance of tobacco. Health screening and early treatment of hypertension and hypercholesterolemia has decreased the incidence of stroke and heart disease, but these efforts need to be expanded to reach all segments of the population. Basic research has opened the door to new therapies aimed at re-establishing blood flow and limiting tissue damage. Clinical trials have already led to changes in stroke prevention, including studies of carotid endarterectomy and ticlopidine and warfarin therapy (for patients with atrial fibrillation). Trials in progress are testing the usefulness of ancrod, neuroprotective agents, antioxidant agents, anti-inflammatory agents, low-molecular-weight heparin, thrombolytic drugs, and angioplasty. Any delay starting therapy after an acute stroke will result in loss of brain tissue. Clinicians should remember that for a stroke patient, time is brain tissue.

### **Antithrombotic agents in cerebral ischemia**

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American Journal of Cardiology (USA), 1995, 75/6 (34B-38B)

The choice of antithrombotic agent in cerebral ischemia depends on the pathogenesis: thrombosis, embolism, or hemorrhage. Antiplatelet agents are considered most beneficial in thrombotic stroke, anticoagulants are most effective in cardioembolic stroke; antithrombotic agents are generally contraindicated in hemorrhagic stroke. A meta-analysis of 18 trials documented a 23% reduction in stroke risk with antiplatelet agents; aspirin is typically the antiplatelet agent of choice for stroke prevention. There are

no definitive data regarding the optimal aspirin dose for stroke prevention and this issue remains controversial. Ticlopidine is the most effective antiplatelet agent, but its adverse effect profile restricts its use. Anticoagulants are highly effective for preventing cardioembolic stroke, but their effectiveness in non-cardioembolic stroke is uncertain because of lack of trial data. Results of the ongoing Warfarin/Aspirin Recurrent Stroke Study (warfarin (INR 1.8-2.8) vs aspirin (325 mg/day)) may clarify this issue. There is renewed interest to indicate that reperfusion within a few hours of stroke onset appears to be effective in preventing neuronal damage. In addition, when given within 6 hours of stroke onset, thrombolytic appear to be relatively safe. Several direct thrombin inhibitors are being evaluated. Experimentally, hirudin, hirulog, D-Phe-L-Pro-L-Arg-CH<sub>2</sub>Cl (PPACK), and argatroban are clearly more effective than heparin in inhibiting platelet deposition and thrombus formation, and also show promise in preventing reocclusion after thrombolysis for both experimental thrombotic and embolic stroke. However, the risk of hemorrhage in patients with cerebrovascular disease is unknown for these agents. New antiplatelet agents, most of which inhibit the platelet IIb/IIIa receptor, have also shown a significant reduction in ischemic complications in experimental thrombosis models.

### **Platelet activity and stroke severity**

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J Neurol Sci 1992 Mar;108(1):1-6

Although platelets constitute the major component of a thrombus, its role in determining the clinical severity of thrombotic stroke is unknown. Therefore, we investigated the relationship between platelet ionized calcium ((Ca<sup>i</sup>)<sub>2+</sub>), a measure of platelet activity and presumably proneness to thrombosis, and clinical stroke severity in 45 consecutively studied acute ischemic stroke patients. Even though there was no correlation between the clinical neurological scores and the levels of baseline and activated platelet (Ca<sup>i</sup>)<sub>2+</sub>, stroke was less severe in patients who had been taking aspirin at the time of stroke onset. These results raise several important questions: (a) is the extent of platelet activation a reflection of thrombus volume, (b) does the clinical severity of neurological deficit reflect the causative thrombus volume, and (c) whether the beneficial effect of aspirin in stroke prophylaxis is through its inhibition of platelets alone.

### **The use of antithrombotic drugs in artery disease**

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Clin Haematol 1986 May;15(2):509-59

Evaluating the use of antithrombotic drugs in artery disease has been a long and difficult process, which is far from complete. The aims of treatment have ranged from the primary prevention of myocardial infarction or stroke, through the restoration of blood flow to ischaemic organs in order to salvage threatened tissue, to the prevention of recurrent vascular occlusion. Drugs studied in depth by clinical trial include the oral anticoagulants, antiplatelet drugs (especially aspirin), and thrombolytic agents. Their results are considered under the headings of coronary artery disease, cerebral ischaemia, and peripheral vascular disease. Aspirin, with or without dipyridamole, prevents progression of unstable angina to myocardial infarction or death, probably reduced long-term mortality after myocardial infarction, and prevents aortocoronary bypass graft occlusion. It of stroke or death in patients with transient cerebral ischaemia, diminishes cardiovascular morbidity after a thrombotic stroke, and may improve the outcome after some kinds of surgery for peripheral vascular disease. The benefits of oral anticoagulant treatment to prevent artery occlusion remain poorly defined. Oral anticoagulants prevent systemic embolism in many groups of high-risk patients, and probably reduce the risk of recurrence after embolism has occurred. Whether their long-term use to prevent reinfarction in patients with a previous myocardial infarct can be justified remains uncertain. They are of little or no proven value in patients with transient cerebral ischaemia or thrombotic stroke. On the other hand, there is increasing support for early thrombolytic treatment after myocardial infarction, especially since two multicentre trials have now shown reduced mortality in patients treated with intracoronary streptokinase within 4-6 hours of infarction and a further large multicentre study also demonstrate reduced mortality in patients treated with early intravenous streptokinase. In addition, the local infusion of streptokinase leads to recanalization in a high proportion of patients with a recent peripheral artery occlusion who are poor candidates for surgery.

### **Medical management in the endovascular treatment of carotid-cavernous aneurysms**

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J Neurosurg 1996 May;84(5):755-61

Carotid-cavernous aneurysms account for between 1.9% and 9.0% of intracranial aneurysms. Entirely intercavernous aneurysms are believed to have a relatively benign course, with cranial nerve findings or headache being the usual initial symptomatology; however, subarachnoid hemorrhage or carotid-cavernous fistula formation can result from rupture. Over the past 15 years endovascular parent artery occlusion has essentially replaced surgical carotid occlusion as the treatment of choice. The authors describe a series of 39 consecutive patients at the University of Virginia Health Sciences Carotid-cavernous aneurysm. Aggressive invasive hemodynamic monitoring and maintenance of a state of normo- to mild hypervolemia in the asymptomatic patient was used throughout the periprocedural period. Rapid institution of hypervolemic-hypertensive therapy can reverse early neurological deficits related to hypoperfusion in these patients. Only one individual managed with this protocol developed neurological deficits not reversible with hypertensive-hypervolemic therapy. Heparin therapy was administered for 48 hours after occlusion, with patients receiving subsequent aspirin therapy for 6 months to combat distal embolism secondary to thrombosis. Long-term complications were not seen in patients receiving aneurysm trapping; however, two individuals with proximal carotid occlusion developed late optic neuropathy and one had recurrent transient ischemic attacks that ceased with supraclinoid carotid clipping.

### **Mechanism of hydrogen peroxide and hydroxyl free radical-induced intracellular acidification in cultured rat cardiac myoblasts**

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Circulation Research (USA), 1996, 78/4 (564-572)

After a transient ischemic attack of the cardiac vascular system, reactive oxygen-derived free radicals, including the superoxide ( $O_2^-$ ) and hydroxyl ( $\cdot OH$ ) radicals can be easily produced during reperfusion. These free radicals have been suggested to be responsible for reperfusion-induced cardiac stunning and reperfusion-induced arrhythmia. Hydrogen peroxide ( $H_2O_2$ ) is often used as an experimental source of oxygen-derived free radicals. Using freshly dissociated single rat cardiac myocytes and the rat cardiac myoblast cell line, H9c2, we have shown, for the first time, that an intriguing  $pH(i)$  acidification (similar 0.24 pH unit) is induced by the addition of 100 micromol/L  $H_2O_2$  and that this dose is without effect on the intracellular free  $Ca^{2+}$  levels or viability of the cells. Using H9c2 as a model cardiac cell, we have shown that it is the intracellular production of  $\cdot OH$ , and not  $O_2^-$  or  $H_2O_2$ , that results in this acidification. We have excluded any involvement of (1) the three known cardiac  $pH(i)$  regulators (the  $Na^+$ - $H^+$  exchanger, the  $Cl^-$ - $HCO_3^-$  exchanger, and the  $Na^+$ - $HCO_3^-$  cotransporter), (2) a rise in intracellular  $Ca^{2+}$  levels, and (3) inhibition of oxidative phosphorylation. However, we have found that  $H_2O_2$ -induced acidosis is due to inhibition of the glycolytic pathway, with hydrolysis of intracellular ATP and the resultant intracellular acidification. In cardiac muscle and in skinned cardiac muscle fiber, it has been shown that a small intracellular acidification may severely inhibit contractility. Therefore, the sustained  $pH(i)$  decrease caused by hydroxyl radicals may contribute, in some part, to the well-documented impairment of cardiac mechanical function (ie, reperfusion cardiac stunning) seen during reperfusion ischemia

### **Thrombolysis of the cervical internal carotid artery before balloon angioplasty and stent placement: Report of two cases**

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Neurosurgery (USA), 1996, 38/3 (620-624)

The application of endovascular techniques to the treatment of cervical carotid artery bifurcation atherosclerosis has been delayed because of the fear of causing embolic events while traversing the diseased portion of the artery with an angioplasty balloon catheter. Symptomatic carotid arteries often contain fresh or partially digested intraluminal thrombus. Before we cross certain carotid bifurcation lesions with angioplasty catheters, we deliver 100,000 to 200,000 units of urokinase in an attempt to digest loose thrombus. We have witnessed changes in the angiographic appearance of the diseased portion of the vessel after urokinase treatment, such as widening of the lumen, that suggest clot lysis. We present two patients who had symptomatic internal carotid artery stenosis. Angiography showed irregular narrowing of the internal carotid artery origin. One patient was selected for angioplasty instead of carotid endarterectomy because of severe cardiac risk factors. The other patient had major angiographic risk factors manifested by poor collateral circulation. The angiographic findings and history of transient ischemic attacks led us to suspect the presence of soft, loose plaque debris or thrombus in both cases. Therefore, we performed thrombolysis with urokinase before angioplasty. Repeat angiography showed widening of the arterial lumen and smoothing of the plaque profile. Subsequent angioplasty and stent placement were uneventful. Intraarterial thrombolysis can produce a change in the angiographic appearance of symptomatic atherosclerotic lesions of the cervical carotid artery bifurcation. Digestion of intraluminal thrombus may provide a safer environment for deployment of endovascular remodeling devices by decreasing the likelihood of embolic phenomena. We believe thrombolysis should be done before angioplasty in select patients.

## **Aspirin at any dose above 30 mg offers only modest protection after cerebral ischaemia**

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Journal of Neurology Neurosurgery and Psychiatry (United Kingdom), 1996, 6 0/2 (197-199)

There is continuing debate about the relative efficacy of low (< 100 mg per day), medium (300 to 325 mg per day), and high (> 900 mg per day) doses of aspirin in patients after a transient ischaemic attack or non-disabling stroke. The purpose of this study was to resolve the issue. Thus a minimeta-analysis was performed on data from 10 randomised trials of aspirin only v control treatment in 6171 patients after a transient ischaemic attack or non-disabling stroke. The data on the trials were listed in an appendix of the report on the second cycle of the Antiplatelet Trialists' Collaboration. There was virtually no difference in relative risk reduction for low, medium, and high doses of aspirin (13%, 9%, and 14% respectively). This equivalence corresponds with the results of the UK-TIA trial in a direct comparison of 300 and 1200 mg. The Dutch TIA trial showed no difference in efficacy of 30 and 283 mg. It is concluded that aspirin at any dose above 30 mg daily prevents 13% (95% confidence interval 4-21) of vascular events and that there is a need for more efficacious drugs.

## **Mild hyperhomocysteinemia and hemostatic factors in patients with arterial vascular diseases.**

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Mild hyperhomocysteinemia, due to genetic or to environmental factors, is now recognized as a risk factor for premature arterial disease, including peripheral arterial occlusion, thrombotic stroke and myocardial infarction. It is defined by either an increased level of fasting homocysteine or by an increased level after loading with methionine, which is more frequently altered than the former. We studied the hemostatic parameters in 88 patients with premature arterial disease (mean age 43 +/- 11 years). We confirmed previously known hemostatic alterations described in vascular patients when compared to controls, but found that, among patients, some of these parameters were more altered in hyperhomocysteinemic patients. When fasting homocysteine was increased, higher alterations were found in factors VIIIc, vonantithrombin complexes were more elevated. When post-methionine load homocysteine was increased, alterations in fibrinolytic parameters were more pronounced.

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