Literaturservice I-GAP
Homocystein

1: Vojnosanit Pregl 2008 Dec;65(12):893-900

Cardiovascular morbidity and mortality in patients treated with hemodialysis--epidemiological analysis.

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BACKGROUND/AIM: Cardiovascular diseases are the leading cause of death in patients treated with hemodialysis (HD). The annual cardiovascular mortality rate in these patients is 9%. Left ventricular (LV) hypertrophy, ischemic heart disease and heart failure are the most prevalent cardiovascular causes of death. The aim of this study was to assess the prevalence of traditional and nontraditional risk factors for cardiovascular complications, to assess the prevalence of cardiovascular complications and overall and cardiovascular mortality rate in patients on HD. METHODS: We investigated a total of 115 patients undergoing HD for at least 6 months. First, a cross-sectional study was performed, followed by a two-year followup study. Beside standard biochemical parameters, we also determined cardiac troponins and echocardiographic parameters of LV morphology and function (LV mass index, LV fractional shortening, LV ejection fraction). The results were analyzed using the Student's t test and Mann-Whitney U test. RESULTS: The patients with adverse outcome had significantly lower serum albumin ($p < 0.01$) and higher serum homocystein, troponin I and T, and LV mass index ($p < 0.01$). Hyperhomocysteinemia, anemia, hypertriglyceridemia and uncontrolled hypertension had the highest prevalence (86.09%, 76.52%, 43.48% and 36.52%, respectively) among all investigated cardiovascular risk factors. Hypertrophy of the LV was presented in 71.31% of the patients and congestive heart failure in 8.70%. Heart valve calcification was found in 48.70% of the patients, pericardial effusion in 25.22% and disrrhythmia in 20.87% of the investigated patients. The average annual overall mortality rate was 13.74%, while average cardiovascular mortality rate was 8.51%. CONCLUSION: Patients on HD have high risk for cardiovascular morbidity and mortality.

2: Pol Merkur Lekarski 2008 Oct;25(148):356-60

[Estimation of relation between homocysteine concentration and selected lipid parameters and adhesion molecules concentration in children with atherosclerosis risk factors]

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Atherosclerosis begins in childhood. At present among numerous risk factors of atherosclerosis the role of hiperhomocysteinemia in development of

cardiovascular heart disease is taken under consideration. Atherogenic effect of homocystein is related to its cytotoxin action, conducting to endothelial dysfunction and damage. It is correlated with increase of the lipid levels in the blood serum and change of expression of the soluble forms of adhesion molecules. The aim of this study was to estimate relations between the homocystein serum concentration, expression of the selected adhesion molecules and the lipid levels in the blood serum in children with atherosclerosis risk factors. MATERIAL AND METHODS: The group consisted of 670 children, 76 of them had atherosclerosis risk factors. In further examination 48 children have taken a part, whose parents were agreed for theirs participation in the program. The comparative group composed of 25 children without the risk factors. We determined total cholesterol (TC), triglycerides (TG), LDL cholesterol fraction (LDL-C), HDL cholesterol fraction (HDL-C), serum homocysteine concentration (Hcy), the expression of the soluble forms of adhesion molecules (sCAM): sP-selectin and sVCAM-1 (vascular cell adhesion molecule-1). RESULTS: Obesity, hypertension and lipid disorders in the shape of higher concentration of TC, LDL-C, TG and lower HDL-C were the most frequent risk factors in the investigated children. No significant differences in serum homocysteine concentration were observed between the investigated groups. However, its concentration was significantly higher in children with two atherosclerosis risk factors. No significant differences in expression of s-VCAM-1 were observed in the investigated groups, concentration of sP-selectin was significantly higher in children with atherosclerosis risk factors ($p<0.05$). Statistically significantly higher serum concentrations of lipid levels were found in children with hyperhomocysteinemia. CONCLUSION: Higher concentration of the serum homocysteine and chosen adhesion molecules in children with atherosclerosis risk factors might potentially constitute the marker of early atherosclerotical risk development.

PMID: 19145936 [found with GoPubMed]

3: Internist (Berl) 2008 Dec;49(12):1507-11

[Thromboembolic events, abortions and a sick infant--unusual presentation of a vitamin deficiency]

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Homocysteine is a risk factor for the development of thromboembolic disorders and vascular diseases. Furthermore, complications during pregnancy have been ascribed to hyperhomocysteinemia. We report on a pregnant woman being substituted by high doses folic acid for hyperhomocysteinemia. Thereby, the underlying pernicious anemia was masked. After birth, the neonate was exclusively breastfed. At the age of 5 months, the infant had to be admitted to hospital due to severe vitamin B(12)-deficiency. Using parenteral vitamin B(12) substitution, homocystein levels of the mother normalized and the infant throve and prospered again.

4: Ter Arkh 2008;80(8):30-8

[Cardiorenal syndrome in ischemic renal disease (atherosclerotic renovascular hypertension)]

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AIM: To characterize cardiorenal syndrome in ischemic renal disease (IRD). MATERIAL AND METHODS: In examination of 105 IRD patients (63 males and 42 females, mean age 63.8 +/- 5.1 years) we estimated body mass index (BMI), indices of peripheral blood and urine, blood biochemistry, glomerular filtration rate (GFR). Plasmic homocystein concentration was measured in 30 patients. We also studied incidence of some cardiovascular risk factors, clinical variants of atherosclerosis and their correlation with GFR. RESULTS: IRD patients most frequently had hypertriglyceridemia (67.6%), hypercholesterinemia (53.3%), smoking (47.1%), obesity (41.9%), metabolic syndrome (38.1%), type 2 diabetes mellitus, arterial hypertension of the third degree (70.6%), isolated systolic arterial hypertension (46.7%). GFR was significantly lower in smokers ($p < 0.001$), arterial hypertension of the third degree ($p < 0.05$), isolated systolic arterial hypertension ($p < 0.001$) and type 2 diabetes mellitus ($p < 0.05$). In GFR < 40 ml/min homocysteinemia increased significantly ($p < 0.01$). Coronary artery disease in IRD occurred in 52.4%, cerebrovascular diseases (brain stroke, transitory ischemic attacks)--in 29.5%, intermittent claudication--in 19.0%, aneurism of the abdominal aorta--in 7.6%, documented atherosclerotic affection of the upper limb arteries--in 2.8%. Patients with intermittent claudication were characterized by significantly less GFR compared to that in patients without clinical symptoms of affected arteries of the lower limbs (38.6 +/- 8.2 and 44.6 +/- 7.3 ml/min, respectively; $p < 0.01$). CONCLUSION: Basic symptoms of cardiorenal syndrome in IRD are high rate of cardiovascular risk factors, some of them provoke aggravation of glomerular endotheliocyte dysfunction and deterioration of intrarenal hemodynamics leading to GFR reduction underlying appearance of new endothelium-tropic risk factors (hyperhomocysteinemia), and progression of atherosclerotic process with formation of its special clinical forms (intermittent claudication).

5: Ann Cardiol Angeiol (Paris) 2008 Aug;57(4):219-24

[Effect of polymorphisms on key enzymes in homocysteine metabolism, on plasma homocysteine level and on coronary artery-disease risk in a Tunisian population]

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BACKGROUND: Hyperhomocysteinemia is known as an independent-risk factor for coronary-artery disease (CAD). However, the effect of homocystein metabolic enzymes polymorphisms on CAD is still controversed. We investigated the relation between homocystein metabolic key enzymes polymorphisms, homocystenemia and coronary stenosis in a Tunisian population. METHODS: Samples were collected from 251 CAD patients documented by angiography. Genotyping were performed for C677T methylene-tetrahydrofolate reductase (MTHFR), A2756G methionine-synthase (MS) and 844ins 68 cystathionine-beta-synthase (CBS). We measured fasting plasma tHcy, folate and vitamin B12. RESULTS: There was significant increase in homocysteinemia for homozygous genotypes of C677T MTHFR ($p<0.001$) and A2756G MS ($p=0.01$), but not for 844ins68 CBS ($p=0.105$). Potential confounders adjusted odds-ratios for significant coronary stenosis, associated with MTHFR TT, MS GG and CBS insertion, were respectively 1.78 ($p=0.041$); 2.33 ($p=0.036$) and 0.87

(p=0.823). The effect of mutated MTHFR genotype was more pronounced on homocysteinemia (21.4+/-9.1 micromol/L; p<0.001) and coronary stenosis (OR=2.73; p=0.033) at low folatemia (< or =6.1 ng/mL). CONCLUSION: MTHFR TT and MS GG genotypes increase tHcy concentration and coronary stenosis risk, especially with low folatemia.

6: Bioessays 2008 Jul;30(7):642-52

The IRBIT domain adds new functions to the AHCY family.

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During the past few years, the IRBIT domain has emerged as an important add-on of S-adenosyl-L-homocystein hydrolase (AHCY), thereby creating the new family of AHCY-like proteins. In this review, we discuss the currently available data on this new family of proteins. We describe the IRBIT domain as a unique part of these proteins and give an overview of its regulation via (de)phosphorylation and proteolysis. The second part of this review is focused on the potential functions of the AHCY-like proteins. We propose that the IRBIT domain serves as an anchor for targeting AHCY-like proteins towards cytoplasmic targets. This leads to regulation of (i) intracellular Ca2+ via the inositol 1,4,5-trisphosphate receptor (IP3R), (ii) intracellular pH via the Na+/HCO3 - cotransporters (NBCs); whereas inactivation of the IRBIT domain induces (iii) nuclear translocation and regulation of AHCY activity. Dysfunction of AHCY-like proteins will disturb these three important functions, with various biological implications.

7: Z Gerontol Geriatr 2008 Jun;

Does an association between increased homocystein levels and cognitive dysfunction also exist in multimorbid geriatric patients?

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BACKGROUND : Total blood homocysteine (Hcys) and folate have been investigated in association with cognitive dysfunction (CD) in healthy but not in multimorbid elderly patients. We hypothesized that total Hcys and folate are adequate markers to identify multimorbid elderly patients with CD. METHODS : According to the Short Performance Cognitive Test (SKT) CD was determined in a cross-sectional study with 189 (131 f/58 m) multimorbid elderly patients with a mean age of 78.6 +/- 7.3 yrs. Besides the analyses of biochemical parameters (Hcys, folate, vitamin B(12), hemogram) nutritional status (BMI, Mini Nutritional Assessment) as well as activities of daily living were assessed. Daily nutritional intake was measured with a 3-day nutrition diary. For analysis, we used the nutritional software program DGE-PC professional. RESULTS : According to SKT 25.4% showed no cerebral cognitive dysfunction, 21.2% had a suspicion about incipient cognitive dysfunction, 12.7% showed mild, 9.0% moderate, 31.7% of patients severe cognitive deficits. Median plasma Hcys was about 20% elevated in

multimorbid elderly patients independent of CD. Serum folate and vitamin B(12) levels were within range, though dietary folate intake (97 [80-128] microg/d) was reduced about 75% (recommendation 400 microg/d). Significant correlations between vitamin intake and plasma/serum levels of Hcys, folate and vitamin B(12) were not present. We did not find significant differences between SKT groups of nutritional status, activities of daily living, index of diseases, medications, or selected biochemical parameters. CONCLUSION : We analysed elevated serum Hcys levels in multimorbid elderly patients with normal plasma folate and vitamin B(12) concentration and CD. Plasma Hcys or serum folate did not appear as an important biological risk factor on CD in multimorbid elderly patients.

8: Rheumatol Int 2008 Jul;28(9):935-7

Henoch-Schonlein purpura with high factor VIII levels and deep venous thrombosis: an association or coincidence?

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Henoch-Schonlein purpura (HSP) is the most common systemic vasculitis in children. Although long-term outcome is generally good, serious complications may occur. Thrombosis has been reported only as an extremely rare complication of HSP. Here, we describe a 15-year-old-boy with features of HSP, who developed left main iliac, external iliac and femoral vein thrombosis. Factor VIII (FVIII) and homocystein levels were found to be high. This suggests that HSP itself may lead to a prothrombotic state and increase the risk of developing thrombosis in patients who have any risk factors.

9: Ter Arkh 2007;79(12):57-62

[Hyperhomocysteinemia--one of the factors underlying thrombotic complications in patients with chronic myeloproliferative diseases]

Sokolova, M A, Khoroshko, N D, Tsvetaeva, N V, Turkina, A G, Levina, A A, Mamukova, Iu I, Rokhnianskaia, A A, Sudarikov, A B, Romanova, E A, Vasil'ev, S A, Sukhanova, G A, Orel, E B, Rudakova, V E, Tutaeva, V V, Manakova, T E, Semenova, E A, Kulikov, S M

AIM: To assess incidence of hyperhomocysteinemia (HHC) in patients with chronic myeloproliferative diseases (CMPD) and to analyse possible correlation between an elevated concentration of plasma homocystein (HC) and thrombotic complications. MATERIAL AND METHODS: The trial enrolled 61 patients: 39 CMPD patients with thrombotic complications and free of them, 22 nonhematological patients with thrombosis. The control group consisted of 40 healthy donors. The examination protocol included determination with standard methods of HC plasma concentration, platelet and plasma components of hemostasis, mutation of factor V Leiden gene, prothrombin and methylenetetrahydrofolate reductase (MTHFR). RESULTS: Mean HC concentration in the serum in CMPD patients was 19 +/- 1.7 mcmol/l which appeared higher than in healthy donors (12 +/- 1.3 mcmol/l). The highest HC was in patients with subleukemic myelosis (SLM)--23 +/- 2.3 mcmol). No difference in HC concentration in plasma was observed in CMPD carriers of homo- or

heteroxygous mutation of C667T gene or CMPD patients without the mutation. In CMPD content of factor VIII was higher in HHC than in normal HC (222 +/- 26.5 and 116 +/- 20%, respectively, p = 0.002). For von Willebrand factor 202 +/- 15.6 and 120 +/- 14.6%, respectively (p < 0.003). HC reduction in response to vitamin therapy was the greater the higher its initial level was. CONCLUSION: There is correlation between HHC and thrombosis in CMPD patients. HC concentration may depend on the proliferative stage of CMPD. As HC is a significant independent factor of thrombotic complications risk, it is necessary to detect and treat HHC.

10: Acupunct Electrother Res 2007;32(1-2):31-70

Anatomical relationship between traditional acupuncture point ST 36 and Omura's ST 36 (True ST 36) with their therapeutic effects: 1) inhibition of cancer cell division by markedly lowering cancer cell telomere while increasing normal cell telomere, 2) improving circulatory disturbances, with reduction of abnormal increase in high triglyceride, L-homocystein, CRP, or cardiac troponin I & T in blood by the stimulation of Omura's ST 36--Part 1.

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Using Bi-Digital O-Ring Test Resonance Phenomena between 2 identical substances, Omura, Y. succeeded in making the image of the outline of internal organs without use of standard imaging devices since 1982. When he imaged the outline of the stomach on the abdominal wall, a number of the lines came out from upper and lower parts of stomach wall. When the lines were followed, they were very close to the well-known stomach meridians. Subsequently, he found a method of localizing meridians and their corresponding acupuncture points as well as shapes and diameters accurately. At the anatomical location of ST 36 described in traditional textbooks, Omura, Y. found there is no acupuncture point. However, in the close vicinity, there is an acupuncture point which he named as true ST 36 in the mid 1980s, but it is generally known as Omura's ST 36. When the effects of the acupuncture on these 2 locations were compared, Omura's ST 36 (true ST 36) produced very significant well-known acupuncture beneficial effects including improved circulation and blood chemistry, while in the traditional ST 36, the effects were small. In this article, the anatomical relationship between these two acupuncture points, with a short distance of 0.6 approximately 1.5 cm between the centers of these locations, was described. In early 2000, Omura, Y. found Press Needle Stimulation of Omura's ST 36, using "Press-Release" procedure repeated 200 times, 4 times a day to cancer patients reduced high cancer cell telomere of 600-1500ng and high Oncogen C-fos Ab2 and Integrin alpha5beta1 of 100-700ng BDORT units to close to lyg (= 10(-24) g) BDORT units. In addition there was a significant reduction of Asbestos and Hg from cancer cells, while markedly reduced normal cell telomere of lyg was increased to optimally high amounts of 500-530ng BDORTunits. Thus, cancer cells can no longer divide and cancer activity is inhibited. The authors have successfully applied this method for a variety of cancers as well as for cardio-vascular diseases with hypertriglyceridemia, hyperglycemia, high L-homocystein, and CRP, high cardiac Troponim I & T, and some hypertension. These beneficial effects were accompanied by euphoria, & relaxation with increased alpha waves in EEG. Thus Omura's ST 36 stimulation is a safe, effective and highly desirable supplemental treatment. In addition to manual stimulation, similar beneficial effects can be induced by finger tip stmulation (without

any needle) or with electroacupuncture stimulation, (+) Qi Gong energy stored paper and (+) solar energy stored paper which often resulted in significant clinical improvement.

11: Georgian Med News 2007 Sep;(150):53-6

[Efficacy and safety of heptral, vitamin B6 and folic acid during toxic hepatitis induced by CCL4]

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The aim of this work was to evaluate of efficacy and safety of complex Heptral, Vitamin B6 and Folic Acid in experimental hepatitis therapy compared with monotherapy. Experiments were carried out on pubertal rats. Eperimental hepatitis models were induced by Tetrachlormethane. The tetrachlormethane intoxication was reproduced by subcutaneous injection of CCL(4) 1ml/kg dissolved in 1ml of olive oil. Cytochrome P450, cytochrome b5, reduced glutation,activity of glutationetranspherase and content of ATP in hepatocytes were measured by the spectrophotometric techniques,but content of homocysteine by chromophtography techniques. Under CCL(4) intoxication disturbance of liver detoxication function, energy deficit and surplus of homocysteine were observed. Treatment of the toxic hepatitis with heptral increased the level of cytochrome P450, cytochrome b5, glutation activity of glutationetranspherase glutathione and reduced content of homocysteine. Complex therapy with Heptral and B6 and folic acid reveal more expressive hepatoprotective effect and safety than monotherapy with Heptral. Complex therapy improves not only the parameters of biotransformation (metabolic and conjugation phase), but also normalizes the level of ATP and homocystein. Vitamins B6 and folic acid increases the efficacy and safety of Heptral. This complex was recomended for treatment of hepatitis.

12: Pol Merkur Lekarski 2007 Feb;22(128):146-9

[Homocystein serum levels and lipid parameters in children with atherosclerosis risk factors]

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Atherosclerosis is a disease of adult patients, however, it begins in childhood and progresses from fatty streaks to raised lesions in arteries in adolescence and young adults. Clinical manifestation of atherosclerosis in adulthood depends on the risk factors such as: lipid disorders, obesity, hypertension, smoking habits and family history of CHD. High serum homocysteine concentration is increasingly recognised as a new risk factor for atherosclerosis and other vascular diseases. Atherogenic effect of homocystein is related to cytotoxin action on the endothelial cells and their function. The aim of this study was to estimate relations between the homocysteine serum concentration and the lipid levels in children with atherosclerosis risk factors. MATERIAL AND METHODS: The study was carried out on 48 children with atherosclerosis risk factors. The control group consisted of 25 healthy childrens. Total cholesterol (TC), Triglycerides

(TG), HDL-C, LDL-C were determined by enzymatic method. Concentration of homocysteine was estimated by immunoenzymatic method (ELISA). RESULTS: Obesity, lipid disorders, and hypertension were the most frequent risk factors in the investigated children. Statistically significant higher concentration of TC, LDL-C, TG and lower HDL-C were observed in children with atherosclerosis risk factors. No significant differences in homocystein concentration were observed in the investigated groups, but homocystein concentration was significantly higher in group of children with atherosclerosis risk factors. CONCLUSION: We observed that increased number of the risk factors is followed by high homocystein concentration in the serum.

13: J Neurol Sci 2007 Jun;257(1-2):255-7

Cryptogenic multi-infarcts and cortico-subcortical dementia in a young adult.

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INTRODUCTION: Etiology of stroke and dementia in young adults are challenging clinical problems, and these diseases often have devastating consequences. We present a case where a final etiologic diagnosis is not possible, in spite of an exhaustive study. CASE REPORT: A 34-year-old man presented with a 5-year history of transient neurological deficits. Examination disclosed a cortico-subcortical dementia, but no other deficits. Laboratory evaluation was unremarkable, including the basic vascular study, homocystein, immunologic study, ACE, serology for Lyme, syphilis and HIV, tests for mitochondrial cytopathy, CADASIL and Fabry's disease, and CSF study. Prothrombotic study was normal except for a heterozygous mutation for factor V Leiden and for methylene tetrahydrofolate reductase. Cardiac exams (electrocardiogram, transesophagic echocardiography and 24 h-ECG) were normal. Cervical and transcranial duplex ultrasound and magnetic resonance angiography (MRA)- were normal, except for a hypoplasic right vertebral artery. Brain magnetic resonance imaging revealed corticosubcortical atrophy and multiple infarcts. The patient was prescribed antiplatelet and statin therapy, and is presently clinically stabilized after 3 years of follow-up, scoring 2 in modified Rankin scale. DISCUSSION: Differential diagnosis of young onset vascular dementia is wide, including a number of rare sporadic and hereditary diseases. Although our case has a heterozygotic mutation for factor V Leiden, this might not explain the whole clinical picture; furthermore, there is no history of other vascular events, as venous thrombosis. An extensive investigation did not lead to a final etiological diagnosis. Nevertheless, even in these cases prevention with antiplatelet and statin might lead to clinical stabilization.

14: Klin Med (Mosk) 2006;84(12):39-42

[Neurological syndromes associated with homocystein dismetabolism]

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The article summarizes the results of clinical, neurological, and laboratory examination of patients with hyperhomocysteinemia. The data

obtained suggest the existence of common pathobiochemical mechanisms of homocystein, cholesterol, and myelin dysmetabolism. The authors demonstrate that neurological manifestations of hyperhomocysteinemia are associated with the processes of demyelinization in the central and peripheral nervous systems.

15: Int J Clin Pract 2007 Apr;61(4):577-82

Gingival health status in renal transplant recipients: relationship between systemic inflammation and atherosclerosis.

Genctoy, G, Ozbek, M, Avcu, N, Kahraman, S, Kirkpantur, A, Yilmaz, R, Kansu, O, Arici, M, Altun, B, Erdem, Y, Bakkaloğlu, M, Yasavul, U, Turgan, C, Kansu, H

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Cardiovascular disease (CVD) is the leading cause of mortality in renal transplant recipients (RTR). Systemic and periodontal inflammation has been suggested to have a possible role in the development of atherosclerosis. In the present study, we aimed to investigate the relationship between gingival health status, inflammation and atherosclerosis in RTRs. Eighty-three RTR (50 male, 33 female) were enrolled in the study. Routine biochemical analyses, serum lipoproteins, C-reactive protein, fibrinogen, homocystein, parathyroid hormone (PTH) and cyclosporin A (CsA) trough levels were studied. All patients had 24-h ambulatory blood pressure monitoring and B-mode ultrasound of the common carotid arteries. Gingival status was evaluated by the Löe and Silness gingival index (GI). Mean GI value was 2.3 +/- 0.5. Fifty patients (60.3%) had GI value >or= 2.1 (severe gingivitis; group A). Thirty-three patients (39.7%) had GI value < 2.1 (no or moderate gingivitis; group B). Age, carotid intima-media thickness (CIMT) and mean time on dialysis before transplantation were significantly higher in group A than in B. Systemic inflammation markers were not different between group A and group B. Mean CIMT was positively correlated with GI (r = 0.425; p = 0.001) and negatively correlated with high-density lipoprotein cholesterol (r = -0.256; p = 0.023). After the correction for confounding variables, mean CIMT was still significantly correlated with GI (r = 0.376, p = 0.02). In RTR, gingival inflammation seems to be associated with CIMT in the absence of systemic inflammation. Thus, gingivitis may, in part, play a role in the development of systemic atherosclerosis without causing any aggravation in systemic inflammatory response.

16: AIDS 2006 Nov;20(17):2159-64

Ezetimibe, a promising lipid-lowering agent for the treatment of dyslipidaemia in HIV-infected patients with poor response to statins.

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OBJECTIVE: To assess the efficacy, safety, and pharmacokinetic interactions of ezetimibe in HIV-infected patients with poorly controlled antiretroviral-associated dyslipidaemia while taking pravastatin alone. DESIGN: A prospective, open-label, one-arm study of 24 weeks duration. PATIENTS AND SETTING: Nineteen patients (18 on stable HAART), with low density lipoprotein (LDL)-cholesterol values of > or = 130 mg/dl despite the use of pravastatin. METHODS: Ezetimibe, 10 mg/day, was added to pravastatin 20 mg/day, while patients maintained the same antiretroviral regimen. Determinations of total, LDL-, and high density lipoprotein (HDL)-cholesterol, triglycerides, apoproteins, and inflammatory factors (homocystein and C-reactive protein) were performed at baseline, and at weeks 6, 12, and 24. Liver enzymes and creatinine phosphokinase were also assessed. Protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) Cmin was determined just before and 12 weeks after ezetimibe introduction. RESULTS: At week 24, 61.5% of patients achieved the endpoint of the study (LDL-cholesterol < 130 mg/dl). Significant declines in mean total and LDL-cholesterol levels were observed between baseline and weeks 6, 12, and 24, irrespective of antiretroviral type (PI or NNRTI). Mean HDL-cholesterol and apoprotein A increased significantly. No patients discontinued therapy due to intolerance or presented toxicity of grade 2 or more. No differences were observed in lopinavir or nevirapine Cmin measured just before and 12 weeks after ezetimibe introduction. CONCLUSION: The addition of ezetimibe to ongoing pravastatin seems to be an effective and safe option for HIV-infected patients not achieving the NCEP ATPIII LDL-cholesterol goals while receiving a statin alone. Its high tolerability and the lack of interactions with the cytochrome CYP3A4 indicate that ezetimibe will not increase the risk of toxicity or pharmacokinetic interactions with antiretrovirals.

17: Prague Med Rep 2006;107(2):227-41

Moderate hyperhomocysteinemia in patients treated for epilepsy.

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Homocystein (Hcy) is regarded as a neuroexcitatory substance, which is therefore used as an epileptogenic agent in experimental epileptology. Experiments "in vivo" as well as "in vitro" revealed its relation to NMDA glutamate receptors, and its potential neurotoxicity. From the clinical aspect, hyperhomocysteinemia (HHcy), mostly as a marker of the risk factor in the vascular damage, was often studied in patients treated with antiepileptic drugs (AE). However, the neuroexcitatory influence of mild HHcy (up to 30 micromol/l) was rarely discussed. Out of a group of 123 adult patients on long-term conventional AE we analyzed 8 patients (7 men and one woman) with moderate to severe HHcy (30.7-109.0 micromol/l) retrospectively and 2-5 years after HHcy normalization. All of them suffered from partial and/or secondary generalized seizures accompanied by neuropsychological impairment depending on the aetiology of the disease. The patients were characterized by a concurrence of several factors: (1) All of them received conventional AEs inducing the cytochrome P 450 at the time HHcy was diagnosed. (2) Molecular-genetic tests showed enzymopathic impairment (methylentetrahydrofolate reductase-MTHFR mutation of the gene C677 T) also in all eight, homozygous in 7 cases and heterozygous in 1 case. (3) All patients were found to have a vitamin deficit or marginal values of at least one of the vitamins under study, especially folate and/or vitamin B6 and 812. With reference to clinical and EEG features, the

potential neuroexcitatory influence of Hcy is discussed taking into account its effect on pathogenetic factors.

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18: Seizure 2006 Dec;15(8):606-9

Capillary microscopy and hemorheology in children during antiepileptic monotherapy with carbamazepine and valproate.

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The interactions of epilepsy and antiepileptic therapy an one hand and cardiovascular system on the other hand are multiple and complex. Antiepileptic drugs (AEDs) cause alterations of serum lipids and of the fatty acid composition of the membranes. Homocystein, known to induce vascular endothelial damage was found to be elevated in patients on valproate (VPA) and carbamazepine (CBZ) therapy. Marked coronary artherosclerosis and myocardial infarction may already occur in children treated with CBZ. Community based studies corroborated a higher incidence of myocardial infarction, peripheral vascular diseases hypercholesterinemia, left ventricle hypertrophy and stroke in patients with epilepsy. In this context, we wanted to elevate changes of microcirculation related to AEDs commonly prescribed such as VPA and CBZ. Capillary microscopy is a non-invasive technique for measuring the velocity of red blood cells and for determining nutritional blood flow in the capillaries of the skin. It can easily be performed in children. The aim of this study was to look for possible effects an antiepileptic monotherapy with carbamazepine or valproate has on the peripheral microcirculation in epileptic children. We were able to examine 14 children with CBZ and 24 children with VPA, recruited in our neuropediatric Unit. The results were compared to normative values, determined in former analyses of 207 healthy children. We found significant differences in capillary density, tortuous index of the capillaries, capillary diameter and flow rate of erythrocytes for both antiepileptic drugs. Additionally, there were changes in plasma viscosity and the aggregation of erythrocytes. These microcapillary effects could be of special interest in the relationship of a long-term antiepileptic therapy and the development of vascular diseases. We suggest that the influence of AEDs on microcirculation should also be considered in further studies on cardiovascular changes in patients with antiepileptic long-term medication.

19: Ter Arkh 2006;78(6):24-30

[The role of hyperhomocysteinemia in systemic lupus erythematosus and antiphospholipid syndrome]

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AIM: To assess the role of hyperhomocysteinemia (HHC) in development of vascular complications in systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS). MATERIAL AND METHODS: A total of 125 participants (24 males and 101 females aged 38 +/- 13 years) were divided into three groups: group 1--SLE patients (n=51); group 2--SLE+APS patients

(n=49); group 3--primary APS patients (n=25). The patients had the disease for 14 +/- 11 years. Lupus anticoagulant (LA) and anticardiolipin antibodies (aCL) marked APS serologically. Homocystein (HC) was assayed by high performance liquid chromatography. HHC (HC > 15 mcg/l) was diagnosed in 82 of 125 (66%) patients: in 59% patients of group 1, 67%--of group 2 and 76%--of group 3. There was a relationship between HHC and digital necrosis (DN): 80% of DN patients had HHC while HHC was diagnosed in 57% patients free of DN (chi-square = 4.76, p = 0.03). Development of occlusions in APS was associated with HHC. Elevated levels of HC in blood was registered in 43 of 55 (78%) APS patients with thromboses vs. 9 of 19 (47%) patients with APS free of thromboses (p = 0.03). HHC occurred significantly more frequently in patients with arterial thromboses (in all 14 patients) than in patients with venous thromboses (in 16 of 23--69.6%, p = 0.03) and in the absence of thromboses (in 9 of 19, 47.4%, p = 0.04). HHC was associated with thromboses of cerebral, peripheral arteries (90 vs. 47% in patients without thrombosis, p = 0.005; 84 vs. 47%, p = 0.04, respectively), coronary vessels (79 vs. 47%, p = 0.04). In APS patients having arterial thromboses with duration of postthrombocytic period (PTP), estimated as time from thrombosis to entering the trial, less than 2 months, HC concentration was significantly higher (22.9 +/- 7.0 mcg/l) compared to patients with PTP more than 2 years (16.6 +/- 3.7 mcg/l (p = 0.04). CONCLUSION: More than 50% patients with SLE and APS, irrespective of APS variants, had an elevated HC level in the blood. Correlation between HHC and development of thromboses, primarily arterial, in APS gives grounds for the role of HHC in development of vascular complications in SLE and APS.

20: Arch Iran Med 2006 Jul;9(3):266-8

The effect of folic acid supplementation in beta-thalassemia major: a randomized placebo-controlled clinical trial.

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Folic acid is a coenzyme for many important biochemical reactions including synthesis of purines, pyrimidines, and nucleoproteins. The recommended daily allowance of folic acid is 65 - 200 microg/day for infants and children. The recommended dose for deficiency states is 1000 microg/day; the effects of excess amounts of folic acid are unknown. The role of folic acid in preventing progression of arteriosclerosis is rather a new issue. Thrombotic events related to slightly elevated levels of homocystein in adults may be decreased by daily consumption of 1 mg of folic acid together with 5 - 100 mg of pyridoxine.

21: Clin Exp Hypertens 2006 Apr-May;28(3-4):191-7

Research actuality in the genetics of stroke.

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Stroke can be viewed as a paradigm for late-onset, complex polygenic diseases. There are two main clinical phenotypes for stroke: ischemic stroke, responsible for 80-90% of stroke events, and hemorrhagic stroke, responsible for the remaining 10-20%. Stroke may either be the outcome of a number of monogenic disorders or, more commonly, a polygenic multifactorial disease. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL), due to mutations in the Notch 3 gene, is the best example of monogenic pathology leading to stroke. The identification of individual causative mutations for polygenic stroke is problematic due to the complexity of such condition. The two main methods of genetic investigation are linkage analyses and association studies, each with advantages and limitations. Associations with polymorphisms in a variety of candidate genes have been investigated, including hemostatic genes, genes controlling homocystein metabolism, the angiotensin-converting enzyme gene, and the endothelial nitric oxide synthase gene. The combination of linkage and association approaches has led to the identification of the first putative gene associated with common polygenic stroke, PDE4D, mapped to chromosome 5q21. The biological revolution of the past years, spurred by the Human Genome Project, promises the advent of novel technologies supported by bioinformatics, which will transform the study of polygenic disorders such as stroke. Understanding the causes of stroke and its effect will allow definition of high-risk populations and make possible specific programs of primary and secondary prevention as well as new therapeutic approaches where prevention has failed.

22: Klin Lab Diagn 2006 Feb;(2):21-2

[An association with the values of homocystein with the course of a postinfarct period in patients of different age]

Chaava, M M, Bukiia, T Sh, Gogokhia, N A

PMID: 16610628 [found with GoPubMed]

23: Clin Chim Acta 2006 Sep;371(1-2):107-11

Evaluation of different bone markers in hemodialyzed patients.

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BACKGROUND: Routinely, nephrologists rely on different biochemical markers like intact PTH (iPTH), bone-specific alkaline phosphatase (BALP), plasmatic calcium and phosphate. The aim of the present study was to evaluate different other bone markers like N-terminal propeptide of type 1 procollagen (P1NP), active isoform 5b of the tartrate-resistant acid phosphatase (TRAP 5b) and beta-crossLaps (CTXS) as well as full-length PTH (wPTH), presumed non-(1-84) PTH, and their ratio in the diagnosis of renal osteodystrophy with high and low turnover. We also determined 25 hydroxyvitamin D (25VTD), 1-25 dihydroxyvitamin D and homocystein (HCY). METHODS: We performed those parameters on 73 patients with end-stage renal disease according to the manufacturers' instructions. RESULTS: There were very strong correlations between the bone markers concentrations, particularly between BALP and P1NP (r=0.953). We did not observe any

correlation between the ratio whole PTH/non-(1-84) PTH and any of the usual bone markers. This ratio was significantly ($p<0.05$) higher in low and high bone turnover patients than in normal patients according to the K/DOQI. We found a correlation between low levels of 25VTD and high levels of HCY. CONCLUSIONS: BALP offers the best clinical and analytical profile as the easier marker of choice in hemodialyzed patients for the diagnosis of bone disease.

24: Transplant Proc 2006 Mar;38(2):413-5

Predictors of vascular access thrombosis among patients on the cadaveric renal transplantation waiting list.

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Acute thrombotic complications remain a constant, proportionally increasing complication before and after renal transplantation. We sought to investigate predictors for a prothrombotic state that increased the risk of vascular access thrombosis, among chronic renal failure patients during the waiting period prior to cadaveric renal transplantation. Chronic renal failure patients awaiting cadaveric renal transplantation and followed between January 2002 and January 2005 were included in this study. The 109 subjects including, 61 females and 48 males of mean age: 47.4 +/- 12.9 years; There were 36 continuous ambulatory peritoneal dialysis and 73 hemodialysis patients. Serum albumin, prealbumin, CRP, d-dimer, fibrinogen, antithrombin III, anticardiolipin antibodies (immunoglobulins G and M), homocystein, vitamin B12, folic acid, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and total platelet count were measured in each patient. Factor V Leiden, prothrombin 20210, ACE and MTHFR gene mutations were studied in all patients. Vascular Access thrombosis was detected in 62 patients. During follow-up 31 of 109 patients died. Vascular access thrombosis occurred in 78 patients who survived and 31 who died. The patients who died showed a significantly higher rate of thrombosis than those who survived (P = .003, OR: 4.61, CI: 1.70 to 12.50). Among the above biochemical risk factors, multiple regression analysis and backward logistic analysis revealed that d-dimer was the strongest biochemical predictor of thrombosis (P = .013, RR: 17.8). Upon evaluation of genetic risk factors, only factor V Leiden mutation was related to vascular access thrombosis (P = .001). In conclusion, the presence of vascular access thrombosis is a risk factor for mortality during the waiting period for cadaveric renal transplantation. As patients with factor V Leiden mutation or high serum d-dimer levels are at high risk for vascular access thrombosis, we recommend close monitorizing of these patients and use of anticoagulant therapy during the waiting period prior to renal transplantation.

25: Isr Med Assoc J 2006 Feb;8(2):103-5

Candidate gene polymorphism in cardiovascular disease: the BIP cohort.

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BACKGROUND: Cardiovascular disease is now well established as a multifactorial disease. In a given individual, the level of cardiovascular risk is due to the interaction between genetic and environmental components. The BIP cohort comprises 3000 patients with cardiovascular disease who were tested for the benefits of bezafibrate treatment. This cohort has the data for the lipid profile of each individual, fibrinogen, insulin, as well as clinical, demographic and lifestyle parameters. OBJECTIVES: To genotype up to 64 variable sites in 36 genes in the BIP cohort. The genes tested in this assay are involved in pathways implicated in the development and progression of atherosclerotic plaques, lipid and homocystein metabolism, blood pressure regulation, thrombosis, rennin-angiotensin system, platelet aggregation, and leukocyte adhesion. METHODS: DNA was extracted from 1000 Israeli patients from the BIP cohort. A multilocus assay, developed by the Roche Molecular System, was used for genotyping. Allele frequencies for some of the markers were compared to the published frequencies in a healthy population (the French Stanislas cohort, n = 1480). RESULTS: Among the 26 comparable alleles checked in the two cohorts, 16 allele frequencies were significantly different from the healthy French population: ApoE(E3, E2, E4), ApoB (71ile), ApoC (3482T, 455C, 1100T, 3175G, 3206G), CETP(405val), ACE (Del), AGT (235thr), ELAM (128arg); P < 0001 and LPL (93G, 291Ser, 447ter); P < 005. CONCLUSIONS: Although a comparable healthy Israeli population study is needed for more precise interpretation of these results, frequency differences in these polymorphic alleles--associated with lipid metabolism, renin-angiotensin system and leukocyte adhesion mechanism--between CVD patients and healthy individuals nevertheless implicate these candidate genes as predisposing for CVD.

PMID: 16544732 [found with GoPubMed]

26: Klin Med (Mosk) 2005;83(11):30-3

[Study of serum levels of homocystein, lipids and their peroxidation products in patients with coronary heart disease]

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The subjects of the study were 30 patients with coronary heart disease (19--with stable, and 11--with instable angina), and 15 practically healthy individuals. The study included measurement of the levels of homocysteine (HC), total cholesterol, cholesterol of low-density lipoproteins, cholesterol of high-density lipoproteins, and lipidperoxidation (LP) products (TBA-reactive products), as well as coagulo-fibrinolytic parameters. The study revealed that patients with instable angina had significantly higher levels of HC and TBA-reactive products compared to those with stable angina and healthy controls. HC level correlated with LP processes in CHD patients (r = 0.55). Methionine loading allowed revealing latent hyperhomocysteinemia.

27: Rev Med Interne 2006 Feb;27(2):106-10

[Factors associated with hyperhomocysteinemia in inflammatory bowel disease: prospective study in 81 patients]

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BACKGROUND: A high prevalence (52%) of hyperhomocysteinemia is observed in Crohn disease (CD), however it is not well documented in ulcerative colitis (UC). Furthermore, in the different works studying hyperhomocysteinemia the associated factors are different. AIM: Prospective evaluation of hyperhomocysteinemia in inflammatory bowel disease (IBD) patients, of the risk factors and the determination of a potential risk of colorectal carcinoma in case of hyperhomocysteinemia. PATIENTS AND METHODS: IBD patients followed in our department were prospectively recruited between November 2003-September 2004. To be included patients should have passed a coloscopy in the two years. Patients with kidney failure or drugs supposed, to interfere with homocystéine metabolism (folates, vitamin B12, methotrexate) were excluded from the study. The following parameters were analysed: age, sex, clinical activity indexes (CDAI for Crohn disease and CAI for ulcerative colitis), length-extent and type of the disease (CD or UC), smoking, plasma homocystein concentration, folates and vitamin B12. RESULTS: Eighty-one patients (60 CD, 21 UC, mean age 43.8 +/- 17.3) were included, 30 had an active disease at inclusion and 16 were smokers. The prevalence of high homocystein concentration was 55.6%. In univariate analysis a low rate of folates was the only risk factor for a high homocystein concentration (74 vs. 52.8%; P = 0.018). Smoking was almost an associated factor. In multivariate analysis, a low rate of folate was the only risk factor of hyperhomocysteinemia, OR = 3.59 [1.27-10.17]. Five endoscopic lesions considered as precancerous were described; these patients had all a hyperhomocysteinemia. CONCLUSION: The prevalence of hyperhomocysteinemia is high in UC and in CD. A low folate rate is the only risk factor observed in our study. There is a possible link between colorectal cancer and hyperhomocysteinemia. A high Plasma homocystein concentration must be search in inflammatory bowel disease patients and a substitutive treatment of folates and vitamin B12 is necessary in case of hyperhomocysteinemia.

28: Ther Umsch 2005 Sep;62(9):641-6

[Homocystein--an independent risk factor for cardiovascular and thrombotic diseases]

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Over the last 20 years homocysteine has taken on increasing importance as an independent, potentially modifiable risk factor for various forms of vascular disease including peripheral and cerebral vascular disease, coronary heart disease and thrombosis. This association has been ascertained in many retrospective and prospective studies but the strength of risk is not yet firmly established although it is clearly dependent on several modifying factors such as other risk factors, nutrition and genetic polymorphisms. Generally it is estimated that hyperhomocysteinaemia is responsible for about 10% of all risks. Homocysteine is formed from the dietary amino acid methionine and plays a pivotal role in folate metabolism and methyl group transfer. Its concentrations in tissues and plasma are influenced by many genetic and environmental factors, especially vitamins such as folate, B12 and B6 as well as certain medications and even life

style factors. Nowadays the measurement of plasma homocysteine is freely available although care has to be taken in sample handling and interpretation of results. Final proof that homocysteine is a causal agent and not just a marker for cardiovascular disease and that reduction of plasma homocysteine by vitamin treatment reduces risk of cardiovascular disease is still awaited. Therefore at the present time neither wide-scale screening for homocysteine levels nor general prophylaxis with high dose vitamins is justified. However most experts recommend homocysteine determination in individuals with existing or high risk for arterial or venous blood vessel disease and their relatives. Elevated homocysteine can be lowered in such cases with a combination of folic acid, vitamin B12 vitamin B6. The results of ongoing trials on the impact of such treatment on risk of vascular disease are awaited with great interest.

29: Georgian Med News 2005 Jun;(123):57-60

[Effect of heptral and folic acid on the hepatic functions during toxic hepatitis]

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The aim of study was to evaluate effectiveness of heptral (S-Adonosylmethionine-Adomet) and folic acid during the acute toxic damage of the liver induced by carbon tetrachloride. Experiments have been carried out on pubertal rats. The carbon tetrachloride intoxication was performed by subcutaneous injection of CCL(4) 1 ml/kg dissolved in 1 ml of olive oil. The activity of aspartat-and alaninaminotransferases, alkaline phosphatase, the content of free and total billirubine in the blood, as well as total oxidant and antioxidant activity of the blood, were measured by the spectrophotometric techniques. Oxidative stress, cytolyses of the hepatocytes and cholestasis were observed during CCL(4) intoxication. Heptral, and in less degree, folic acid improved liver function during the acute toxic damage, but complex therapy with heptral and folic acid revealed more expressive hepatoprotective effect. It is suggested that better positive effect of complex therapy with heptral and folic acid compared with monotherapy by each drug is probably associated with resynthesis of methionine from homocystein (toxic metabolite of adenosylmethionine) by folate. This combination allows reducing the side effects of heptral induced by homocysteine.

30: Clin Hemorheol Microcirc 2005;33(1):41-6

Plasma total homocysteine concentrations in obese and non-obese female patients with type 2 diabetes mellitus; its relations with plasma oxidative stress and nitric oxide levels.

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Hyperhomocysteinemia has been identified as independent risk factor for early atherosclerotic vascular disease. The purpose of our study was to investigate the plasma homocystein (Hcy) concentrations and its relationship with lipid peroxidation as thiobarbituric acid reactive

substances (TBARS) and nitric oxide (NOx; nitrite plus nitrate) concentrations in age-matched non-obese (n=55) and obese (n=60) female subjects with type 2 diabetes mellitus. Non-obese diabetic patients have significantly higher plasma tHcy and TBARS ($p<0.001$ and $p<0.001$), and significantly lower NOx concentrations than the controls (n=25) ($p<0.001$). The plasma tHcy and TBARS concentrations were higher and nitric oxide concentrations were lower in obese diabetics than in non-obese diabetics (for each comparison; $p<0.001$). Correlation analysis demonstrated that there was a significant positive correlation between tHcy and TBARS ($r=0.452$, $p<0.01$) in diabetics groups. There was no significant correlation between tHcy and plasma NOx, insulin and blood pressure. We thought that Hcy might have a permissive role on the endothelium damage through free radical generating systems and the presence of obesity the free radical induced-damage has been elevated in diabetic patients.

31: Diabet Med 2005 Jul;22(7):871-6

Impaired vascular function during short-term poor glycaemic control in Type 1 diabetic patients.

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AIM: To study the effects of short-term poor glycaemic control on vascular function in Type 1 diabetic patients. METHODS: Ten Type 1 diabetic patients, with diabetes duration of less than 10 years and normal urinary albumin excretion and ophthalmoscopy, were studied. All patients were examined after 48 h of good vs. poor glycaemic control within a 3-week period. Blood glucose was measured seven times daily for 2 days before each examination. External ultrasound was used to measure the dilatory response of the brachial artery to post-ischaemic increased blood flow (endothelium-dependent dilation) and to nitroglycerin (endothelium-independent dilation). Plasma concentration of von Willebrand factor antigen, adhesion molecules, vascular endothelial growth factor, homocystein and cholesterol were also measured. RESULTS: The median blood glucose levels in the 48 h before the examinations were [median (range), good vs. poor control]: 6.3 (5.0-7.6) vs. 15.9 (11.3-17.8) (mmol/l). The flow-associated vasodilation (% of baseline) was reduced during poor control: 102.7 (94.7-110.8) vs. 104.0 (99.6-118.5) ($P < 0.05$) as were the nitroglycerin-induced dilation (% of baseline): 114.5 (103.3-127.9) vs. 120.2 (106.8-148.0) ($P < 0.05$). P-von Willebrand factor antigen was high during poor control (kIU/l): 1.14 (0.73-1.84) vs. 0.86 (0.72-1.39) ($P < 0.05$) and so was P-vascular endothelial growth factor (ng/l): 288 (133-773) vs. 254 (90-383) ($P < 0.05$). CONCLUSIONS: Short-term (48 h) hyperglycaemia in Type 1 diabetic patients may disturb vascular function, possibly mediated through smooth muscle cell dysfunction as well as endothelial dysfunction. We suggest that prolonged and repeated episodes of hyperglycaemia could possibly lead to permanent vascular dysfunction and thereby development and progression of vascular complications in diabetes.

32: Prev Med 2005 May;40(5):583-8

Job stress and cardiovascular risk factors in male workers.

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BACKGROUND: This study examined whether job stress (work demand and decision latitude) is associated with smoking, blood pressure, lipid level (total cholesterol, triglyceride, HDL cholesterol), and homocystein as risk factors for cardiovascular disease in Korean male workers. METHODS: Study subjects of this study were recruited from a sample of 1,071 workers in 20 companies of W city and H counties, and they were grouped into four categories (high strain group, active group, passive group, and low strain group) based on the postulation of Karasek's Job Strain Model. Of them, we invited 160 male workers (40 people each subgroup) using a stratified sampling, and finally, 152 eligible participants were analyzed. RESULTS: In multivariate analyses, we found that decision latitude was associated with cholesterol, triglyceride, and homocystein and that work demand was related to smoking and systolic blood pressure. Job strain (the combination of high work demand with low decision latitude) was significantly related to higher levels of homocystein after controlling for age, BMI, smoking, and social support at workplace. CONCLUSIONS: These results indicate that job stress is associated with cardiovascular risk factors and might contribute to the development of cardiovascular disease. Some considerations for the future research were discussed.

33: Praxis (Bern 1994) 2004 Dec;93(50):2093-7

[Homocystein and cardiovascular risk: is dosage useful?]

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Hyperhomocysteinemia represents an independent risk factor for atherothrombotic disease. Physiopathological mechanisms of accelerated progression of atherosclerosis in presence of hyperhomocysteinemia are complex. Herein we report a clinical case which emphasis the importance of screening elevated homocystein in the absence of conventional risk factors in patients who suffer from premature atherosclerosis.

34: Metabolism 2005 Jan;54(1):72-8

Does the type of hormone replacement therapy affect lipoprotein (a), homocysteine, and C-reactive protein levels in postmenopausal women?

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BACKGROUND: The results of studies evaluating the effect of hormone replacement therapy (HRT) on the cardiovascular risk raise many controversies. This may be related to both the type of treatment used and the disregard of additional risk factors. OBJECTIVE: The objective of the study was to evaluate the effect of natural estrogens taken transdermally

and synthetic estrogens taken orally on the concentrations of lipoprotein (a) [Lp(a)], homocysteine, and C-reactive protein (CRP) in healthy women in the early postmenopausal period. Material The study was conducted on 61 healthy women with average age of 52.3 +/- 4.1 years, in the postmenopausal period, who were randomly assigned to 3 groups depending on the type and route of administration of the products. Group I (n = 24) was administered transdermal estrogens (micronized 17beta-estradiol; Systen, Janssen-Cilag, Switzerland) and progesterone in the second phase of the cycle. Group II (n = 21) was administered oral hormones (Cyclo-Menorette). Group III (n = 16), serving as a control, included women taking placebo in the form of patches. In each group, therapeutic cycles took 22 days and were followed by a treatment-free interval of 7 to 10 days for a 3-month period. RESULTS: After 3 months of treatment, Lp(a) and homocysteine levels were not significantly different from the baseline, irrespective of the route of administration of estrogens or placebo. Both forms of HRT used indicate significant difference in changes of CRP concentration during 3 months of administration (analysis of variance P = .0356). CRP concentration values increased in the group of women using oral HRT from 1.22 to 2.68 mg/L. In the group of women using oral therapy, significantly more cases (61%) of increase in CRP concentration compared with 39% in the transdermal HRT group (chi(2) P = .015) were observed. CONCLUSIONS: On the basis of our observations, it appears that in women in the early postmenopausal stage with normal initial concentrations of Lp(a) and homocystein, the form of therapy used has no influence on values of these parameters. The 2 forms of HRT therapy differ in effect, which is expressed as a change in CRP concentration. A tendency to increase CRP values when using oral HRT is observed, while such an effect is not observed in case of transdermal therapy after 3 months.

35: Rom J Intern Med 2002;40(1-4):61-73

Effects of Atorvastatin on some inflammatory parameters in severe primary hypercholesterolemia.

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Recent publications have reanimated the point of view that there exist links between atherosclerosis--inflammation and hypercholesterolemia. The aim of our study was to investigate the possible influence of statins on some inflammatory parameters in persons with severe primary hypercholesterolemia (PHC). The effects of the HMG CoA reductase inhibitor--Atorvastatin--on serum lipids, apoproteins, C reactive protein (CRP), soluble Intercellular Adhesion Molecule (sICAM), lipid peroxides, antibodies to oxidized LDL (Ab oxLDL) and homocystein were evaluated in 21 persons (52.9 +/- 8.38 years old) with severe PHC, 12 of these having significant coronary-artery stenosis (diameter stenosis > or = 70%), in at least one major coronary artery branch. Ab oxLDL, sICAM, TBARS, CRP and homocystein were significantly increased ($p < 0.05$) in patients with coronary-artery stenosis. Following a 4 weeks hypolipemiant free baseline period, all persons were treated with Atorvastatin 40 mg once daily for 8 weeks. Atorvastatin 40 mg resulted in a reduction of LDL-C with 57.8% (baseline 259.6 +/- 71.39 mg%) $p < 0.001$, total Cholesterol with 44.08% (baseline 343.1 +/- 71.72 mg%) $p < 0.001$, Apo B with 50.6% (baseline 194.7 +/- 48.71 mg%) $p < 0.001$, TG with 12.02% (baseline 177.4 +/- 83.63 mg%) and HDL-C was increased with 6.84% (baseline 48.0 +/- 7.86 mg%). In coronary heart disease patients, Atorvastatin reduced homocystein concentrations with 19.41% (baseline 17.7 +/- 11.16 microM/l) ($p < 0.01$), and CRP with

21.9% (baseline 4.8 +/- 4.19 mg/l) p < 0.01 and TBARS with 52% (baseline 0.87 +/- 0.89 nM/ml) p < 0.001, but did not influence sICAM and Ab oxLDL. Thus atherogenic concentrations of LDL-C have to be closely modulated by minimal changes in LDL oxidative state. The effects of Atorvastatin on inflammatory parameters may crucially contribute to the clinical benefit of statins, independent of cholesterol lowering. Plaque stabilization may be a paradigm for antiinflammatory mechanism of action by this class of drugs.

36: Ter Arkh 2004;76(6):67-70

[Hyperhomocysteinemia and acute phase proteins in various forms of ischemic heart disease]

Paramonov, A D, Moiseev, S V, Fomin, V V, Kopeleva, M V, Stankevich, L I, Martynov, A I, Mukhin, N A

AIM: To determine clinical significance of high concentrations of homocystein, C-reactive protein, fibrinogen in various forms of ischemic heart disease. MATERIAL AND METHODS: Enzyme immunoassay was made to measure serum concentrations of homocystein, C-reactive protein, fibrinogen in 60 patients with ischemic heart disease (IHD) in the form of stable effort angina (n = 20), painless myocardial ischemia (n = 19), unstable angina pectoris (n = 21) and 20 control patients free of IHD. Myocardial ischemia was confirmed at dobutamine stress echocardiography. RESULTS: Serum concentrations of homocysteine, C-reactive protein and fibrinogen were higher in patients with unstable angina than in the other examinees with IHD. A statistically significant correlation exists between homocysteine serum levels and acute phase proteins (C-reactive protein, fibrinogen) in patients with unstable angina. In the other groups it was absent. CONCLUSION: Correlation between serum levels of homocysteine and acute phase proteins in patients with unstable angina suggests a direct participation of this amino acid in destabilization of atherosclerotic plaques and development of acute coronary syndromes.

38: Rev Med Interne 2004 Aug;25(8):556-61

[Update of pernicious anemia. A retrospective study of 49 cases]

Loukili, N H, Noel, E, Blaison, G, Goichot, B, Kaltenbach, G, Rondeau, M, Andrès, E

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PURPOSE: The aim of this study was to describe the present clinical characteristics of the pernicious anemia (PA). METHOD: It is a retrospective (1996-2002) multicenter (five departments of internal medicine) study of 49 patients presenting an established cobalamin deficiency related to PA. RESULTS: The median age of the patients was 74 years (25-93), the female/male ratio 2:9. Several autoimmune disorders were noted in 35% of the patients. Various clinical manifestations, mainly neurological, cutaneous and thrombotic, were found in 65.4% of the patients, at least one hematological abnormalities in 100%. Average serum

vitamin B12 and homocystein levels were with 73 pg/ml (20-1960) and 42.9 micromol/l (7, 8-124). Anti-intrinsic factor or anti-parietal gastric cells antibodies were found in 87.5% and 62% of the patients (at least one antibody, in 96%) abnormal Schilling's test results in 86%. All the followed patients were successful treated with intramuscular (n = 27) or oral crystalline cyanocobalamin (n = 5). CONCLUSIONS: PA was associated with several autoimmune disorders; PA may be responsible of various clinical manifestations or biological abnormalities; and oral crystalline cyanocobalamin treatment may be successful.

39: Ther Umsch 2004 Feb;61(2):93-102

[Conventional and new laboratory parameters in the evaluation of hematologic disease]

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Laboratory investigation plays a crucial role in the workup of hematological disease. The well established method of morphological analysis of blood components has been continuously complemented by other methods. On one hand, these consist of considerable improvements of methods employed for automated cell enumeration allowing for early and accurate detection of cell subpopulations, and quantification of valuable red cell parameters, which are of use in the differential diagnosis of anemia. On the other hand, several parameters for the differentiation of microcytic anemia have become available often allowing for the sometimes difficult diagnosis of anemia of chronic disease, iron deficiency anemia, or thalassemia (ferritin, soluble transferrin receptor, transferrin saturation, RDW, zinc protoporphyrin, as well as reticulocyte indices CHr, Ret-Y Hypo%). In macrocytic anemia, introduction of methods to measure methylmalonic acid (MMA), homocystein, holotranscobalamin (holo-TC), complement the determinations of vitamin concentrations (vitamin B12, folic acid in serum and erythrocytes). Employing these newer parameters in addition to the well established ones allows for detection of early or combined disease. The clinician has to know the diagnostic characteristics not only of the old but also of the newer parameters.

40: J Chromatogr B Analyt Technol Biomed Life Sci 2004 Feb;800(1-2):275-80

Liquid chromatographic determination of total homocysteine in blood plasma with photometric detection.

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A rapid and sensitive method for quantification of homocysteine total forms and glutathione levels in blood plasma via HPLC was developed. Dithiotreitol as a water soluble agent has been used as a reductant for both protein and nonprotein disulphides. Dithiotreitol reacts with the mixed disulphides under 60 degrees C treatment within 10 min. Reduced aminothiols and homocystein were easily derivated with 5,5'-dithiobis-(2-nitrobenzoic acid) and the resultant ultraviolet absorbance within 330 nm

was detected by the HPLC method. The concentration of total plasma homocysteine was significantly higher in groups of patients: with the end stage of renal disease: 45.5+/-40.9 micromol/l (n=79), with cerebral vascular disorders 12.3+/-7.0 micromol/l (n=65), and with coronary atherosclerosis 15.4+/-10.9 micromol/l (n=15) than that in healthy subjects (6.2+/-1.74 micromol/l, n=20). Some major advantages of the method include: simultaneous measurement of both total homocysteine and total glutathione, no loss of oxidized form during processing of blood plasma for aminothiols measurement, use of protein-bound aminothiols solution as a calibrator.

41: Clin Chem Lab Med 2003 Nov;41(11):1392-403

DACH-LIGA homocystein (german, austrian and swiss homocysteine society): consensus paper on the rational clinical use of homocysteine, folic acid and B-vitamins in cardiovascular and thrombotic diseases: guidelines and recommendations.

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About half of all deaths are due to cardiovascular disease and its complications. The economic burden on society and the healthcare system from cardiovascular disability, complications, and treatments is huge and getting larger in the rapidly aging populations of developed countries. As conventional risk factors fail to account for part of the cases, homocysteine, a "new" risk factor, is being viewed with mounting interest. Homocysteine is a sulfur-containing intermediate product in the normal metabolism of methionine, an essential amino acid. Folic acid, vitamin B12, and vitamin B6 deficiencies and reduced enzyme activities inhibit the breakdown of homocysteine, thus increasing the intracellular homocysteine concentration. Numerous retrospective and prospective studies have consistently found an independent relationship between mild hyperhomocysteinemia and cardiovascular disease or all-cause mortality. Starting at a plasma homocysteine concentration of approximately 10 micromol/l, the risk increase follows a linear dose-response relationship with no specific threshold level. Hyperhomocysteinemia as an independent risk factor for cardiovascular disease is thought to be responsible for about 10% of total risk. Elevated plasma homocysteine levels (>12 micromol/l; moderate hyperhomocysteinemia) are considered cytotoxic and are found in 5 to 10% of the general population and in up to 40% of patients with vascular disease. Additional risk factors (smoking, arterial hypertension, diabetes, and hyperlipidemia) may additively or, by interacting with homocysteine, synergistically (and hence over-proportionally) increase overall risk. Hyperhomocysteinemia is associated with alterations in vascular morphology, loss of endothelial anti-thrombotic function, and induction of a procoagulant environment. Most known forms of damage or injury are due to homocysteine-mediated oxidative stress. Especially when acting as direct or indirect antagonists of cofactors and enzyme activities, numerous agents, drugs, diseases, and lifestyle factors have an impact on homocysteine metabolism. Folic acid deficiency is considered the most common cause of hyperhomocysteinemia. An adequate intake of at least 400 microg of folate per day is difficult to maintain even with a balanced diet, and high-risk groups often find it impossible to meet these folate requirements. Based on the available evidence, there is an increasing call for the diagnosis and treatment of elevated homocysteine levels in high-risk individuals in general and patients with manifest vascular disease in particular. Subjects of both populations should first have a baseline homocysteine assay. Except where

manifestations are already present, intervention, if any, should be guided by the severity of hyperhomocysteinemia. Consistent with other working parties and consensus groups, we recommend a target plasma homocysteine level of <10 micromol/l. Based on various calculation models, reduction of elevated plasma homocysteine concentrations may theoretically prevent up to 25% of cardiovascular events. Supplementation is inexpensive, potentially effective, and devoid of adverse effects and, therefore, has an exceptionally favorable benefit/risk ratio. The results of ongoing randomized controlled intervention trials must be available before screening for, and treatment of, hyperhomocysteinemia can be recommended for the apparently healthy general population.

42: Clin Nephrol 2003 Sep;60(3):168-75

Neither folic nor folinic acid normalize homocysteine levels in hemodialysis patients.

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AIMS: A greater decrease in total homocystein (tHcy) has been reported in patients on hemodialysis (HD) following the administration of reduced forms of folic acid (FA), however, the effect of the administration of moderated doses of oral levofolinic acid has not been compared with that of FA. We decided to perform a study to evaluate the therapeutic effectiveness of oral levofolinic acid, the pharmacologically active form of folinic acid in our population of HD patients already on treatment with oral FA and vitamin B6. MATERIAL AND METHODS: We undertook a prospective study in HD patients who had been receiving oral supplements of both FA 5 mg every 48 hours and vitamin B6 40 mg every 7 days during at least 6 months, with a 17% initial decrease of tHcy levels. Patients matched for age, sex and time on HD were assigned to 1 of 2 groups: Those in group A continued to receive their previous supplements while in group B, FA was substituted by calcium levofolinate 5 mg given orally every 48 hours. The following parameters were measured at baseline and at month 6: urea kinetic model and concentrations of plasma albumin, C-reactive protein, folate, vitamin B12, pyridoxal phosphate and tHcy. RESULTS: Group A: 30 patients aged 63.4 (57.9, 68.9) years, with a time on HD of 23.4 (15.8, 30.8) months, group B: 32 age-matched patients 66.2 (62.1, 70.3) years old, with a time on HD of 23.8 (16.7, 30.9) months. No differences were found either in folate levels (72.7 (47.9, 97.5) vs. 71.9 (44.0. 99.9) ng/ml), tHcy (23.5 (21.1, 25.9) vs. 23.3 (20.8, 25.8) micromol/l), or any other study variables. In the 2 groups a significant reduction in both residual renal function (RRF) and vitamin B12 levels was observed after supplementation, but no changes in tHcy values, folate levels or any of the other parameters were found. The prevalence of hyperhomocysteinemia in group A was 93.3% at study start and 100% at month 6, in group B the corresponding values were 93.8% and 96.9%. After 6 months, multiple regression analysis showed that tHcy levels were not influenced by the type of treatment (p = 0.543). CONCLUSIONS: After 6 months of calcium-levofolinate supplementation tHcy levels did not decrease and were similar to those in patients given the same dose of FA.

44: Rev Med Interne 2003 Apr;24(4):218-23

[Vitamin B12 deficiency with normal Schilling test or non-dissociation of vitamin B12 and its carrier proteins in elderly patients. A study of 60 patients]

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PURPOSE: Approximately 15% of people over 60 years old have a cobalamin (Cbl) deficiency in relation with a food-cobalamin malabsorption (FCM). But to date, only case reports or small series have been reported. The aim of this study was to describe the clinical characteristics of the FCM in old subjects. METHODS: Sixty patients, at least 65 years old, presenting a Cbl deficiency related to FCM, were extracted from a cohort study of the Hôpitaux universitaires de Strasbourg, France (n = 169). All these patients had an established diagnosis of Cbl deficiency and met the Carmel's criteria of FCM. Their clinical data were retrospectively analysed. RESULTS: The median age of the 60 patients was 75 years and the female/male ratio was 2.3. The principal clinical symptoms were peripheral neuropathy (35%), confusion and dementia (30%) and anemia-related manifestations such as asthenia and edemas of the legs (20%). Average hemoglobin was 10.7 +/- 2.5 g/dl and average mean erythrocyte cell volume was 95.5 +/- 13.8 fl. There was an anemia, a leucopenia, a thrombocytopenia and a pancytopenia in respectively 27%, 18%, 15% and 8% of the cases. Average serum vitamin B(12) and homocystein levels were with 138 +/- 42 pg/ml and 22.5 +/- 15.2 micro mol/l. No patient had anti-intrinsic factor antibody and the Schilling's test was normal in all patients. Main disorders associated with FCM were atrophic gastritis (59%), long-term metformin or antiacid intake (17%), chronic alcohol intake (8%) and idiopathic FCM (n = 10). Sixteen patients have been successfully treated with oral crystalline cyanocobalamin (500 +/- 280 micro g/d). CONCLUSIONS: This study shows that: firstly, the Cbl deficiency related to FCM may be responsible of severe neurological and hematologic manifestations in approximately 20% of the elderly patients; secondly, the disorders associated with the FCM are multiple in old age, with mainly atrophic gastritis; and thirdly, in clinical practice, oral cyanoCbl treatment may be successful.

45: Ann Biol Clin (Paris) 2002 Sep-Oct;60(5):549-57

[Homocysteine, lipoprotein (a): risk factors for coronary heart disease]

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Our data suggest that the hyperhomocysteinemia and/or increased plasma level of lipoprotein Lp(a) are risk factors for coronary heart disease. We investigated 178 patients who underwent complete cardiac examination comprising coronary angiography and biological analysis (CT, HDL-c, LDL-c, TG, and apoAI, apoB, homocysteine and Lp(a)). Patients presenting a significant stenosis of the coronary artery (50% of the vascular lumen) were considered as cases (113 patients). Those without stenosis or with non-significant stenosis (< 50% of the vascular lumen) were used as controls (65 subjects). Homocysteinemia was significantly higher in cases than in control subjects (8.26 mol/L (2.34 versus 17.85 (2.34, p < 0.001). A strong association between coronary heart disease and homocystein has

been found (Eta(2) = 0.76). The OR were 0.16 when homocystein level was lower than 15 mol/L, and 27.78 when homocysteine level was upper than or equal to 15 mol/L. The RR was 5.16 (95% IC = 3.66-6.66, p < 0.001). Even though there was a significant correlation between tabagic impregnation and homocysteinemia (Spermann's rho = 0.37, p < 0.05), there was no interactive effect between these two factors and coronary disease (Wald khi2 = 0.086, p > 0.05). Therefore, no association was found between homocyteinemia and other coronary heart disease risk factors. The Lp(a) levels were significantly higher in cases than in controls subjects (188 (84 mg/L in control subjects versus 590 (199 in cases, p < 0.001). A stronger relationship was noted between coronary heart disease and Lp(a) (Eta (2) = 0.66). The OR were 0.09 when lipoprotein (a) levels were lower than 350 mg/L, and 5,88 when Lp(a) levels were higher than or equal to 350 mg/L. The estimate RR was 6.47 (95% IC = 4.39-8.55, p < 0.001). The level of Lp(a) was positively correlated with the severity of coronary heart disease (Spermann's rho = 0.95, p < 0.001). A weak correlation between Lp(a) and LDL-c was observed (Spermann's rho = 0.12, p = 0.048). But the multivariate analysis didn't show interactive effect between these two factors and coronary disease (khi2 de Wald = 0.264, p > 0.05). No association was noted between Lp(a) and the others risk factors. Moreover, a positive correlation between the levels of homocysteine and those of Lp(a) was found (Spermann's rho = 0.54, p < 0.001). In contrast their effect on coronary heart disease seems to be independant (Wald khi2 = 2.957, p > 0.05). Thus, these two parameters appear as independant risk factors for coronary heart disease.

46: Minerva Med 2002 Aug;93(4):275-86

[Cardiovascular prevention: new biochemical plasmatic markers of risk]

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The primary prevention of acute coronary syndromes is an open question. The scientific progress has discovered new biochemical markers of cardiovascular disease risk that may be useful for primary prevention. They are plasmatic markers of inflammation (serum amyloid A, C-reactive protein, phospholipase A2) and of infection (seropositivity to Chlamydia pneumoniae, cytomegalovirus). They are plasmatic markers of endothelial activation (adhesion molecules such as ICAM-1, VCAM-1) immunological markers (autoantibodies against oxydized LDL, hemostatic markers (TFPI, PAI-1) and metabolic indices (Lpa, homocystein). A gap is evident between the scientific progress in the knowledge of the epidemiology of cardiovascular pathology and its application in clinical practice. The priority should become the population approach to primary prevention: the rapidly changing and complex global context presents new challenges for public health practitioners struggling to implement preventive policies and programmes. New risk factors of cardiovascular disease have been pointed out by research. This study shows the situation on the topic with critique and updated analysis.

47: Orv Hetil 2002 Jul;143(27):1635-40

[Frequency of hyperhomocysteinemia in hemodialysis patients with folic acid supplementation]

Kárpáti, István, Balla, József, Szóke, Gabriella, Bereczky, Zsuzsanna, Páll, Dénes, Ben, Thomas, Toma, Kornél, Katona, Evelin, Mohácsi, Attila, Paragh, György, Varga, Zsuzsa, Kakuk, György, Muszbek, László

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BACKGROUND: It is known that hyperhomocystinemia is an independent risk factor for development of atherosclerosis. In end stage renal disease the frequency of hyperhomocystinemia is much greater than in normal populations. AIM: In this study homocystein (Hcy), folic acid and vitamin B12 concentrations were determined in 125 chronic renal failure patients being on folic acid supplementation (3 mg/day). In 107 patients the frequency of C667T polymorphism of methylene tetrahyrofolate reductase (MTHFR) was also determined. The relationships between these parameters were also studied. RESULTS: It was found that in these patients who are under continuous folic acid supplementation the mean level of homocysteine was 16.8 +/- 7.2 mumol/L, a value considerably lower than the homocysteine concentration reported for non-supplemented patients. The elevation of homocysteine concentrations was independent of gender, time spent in renal replacement therapy, and the type of renal replacement therapy (hemodialysis: 17.6 +/- 12.6; hemodiafiltration: 16.6 +/- 12.9 mumol/L). Data showed an inverse relation between plasma homocysteine concentrations and the concentrations of folic acid and vitamin B12. Moderately severe hyperhomocystinemia (Hcy > 20 mumol/L) was found in about 30% of patients. In those the frequency of patients for homozygous T677 allele of MTHFR was about 25-30%. However, in all ESRD patients the frequency of the homozygotes was the same then in the normal population. Homocysteine plasma levels correlated with MTHFR polymorphism: in the wild type group Hcy was 14 +/- 7 mumol/L, in the heterozygous group was 17.2 +/- 6.2 mumol/L, and in the homozygous group was 21 +/- 19 mumol/L. CONCLUSIONS: Long-term folic acid supplementation decreased the homocysteine level in end stage renal disease patients. However, in folic acid resistant group, who were in 30% homozygotes for C667T of MTHFR (suggesting that homocysteine-methionine remethylation cycle is disturbed), instead of the administration of folic acid, methylene tetrahydrofolate supplementation might be considered.

48: Lipids 2001;36 Suppl:S27-32

Short-term folic acid supplementation induces variable and paradoxical changes in plasma homocyst(e)ine concentrations.

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Folic acid is presently the mainstay of treatment for most subjects with elevated plasma homocyst(e)ine concentrations [Plasma or serum homocyst(e)ine, or total homocysteine, refers to the sum of the sulfhydryl amino acid homocysteine and the homocysteinyl moieties of the disulfides homocystine and homocystein-cysteine, whether free or bound to plasma proteins.] Changes in homocyst(e)ine in response to folic acid supplementation are characterized by considerable interindividual variation. The purpose of this study was to identify factors that contribute to heterogeneity in short-term responses to folic acid supplementation. The effects of folic acid supplementation (1 or 2 mg per day) for 3 wk on plasma homocyst(e)ine concentrations were assessed in 304 men and women. Overall, folic acid supplementation increased mean plasma

folate 31.5 +/- 98.0 nmol/L and decreased mean plasma homocyst(e)ine concentrations 1.2 +/- 2.4 micromol/L. There was evidence of substantial interindividual variation in the homocyst(e)ine response from -18.5 to +7.1 micromol/L, including an increase in homocyst(e)ine in 20% of subjects (mean increase 1.5 +/- 1.4 micromol/L). Basal homocyst(e)ine, age, male gender, cigarette smoking, use of multivitamins, methylene tetrahydrofolate reductase, and cystathionine beta-synthase polymorphisms accounted for 47.6% of the interindividual variability in the change in homocyst(e)ine after folic acid supplementation, but about 50% of variability in response to folic acid was not explained by the variables we studied.

49: Med Sci Monit 2001 Nov-Dec;7(6):1242-9

Elevated concentrations of homocysteine in children and adolescents with arterial hypertension accompanying Type 1 diabetes.

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BACKGROUND: Ischemic heart disease is the primary cause of morbidity and mortality among diabetics, especially those who became ill at a young age. In evaluating the risk of the development of atherosclerotic changes, especially when occurring prematurely, increasing attention is being paid to new, unconventional risk factors. One of many such new factors, and one whose role in the development of atherosclerotic changes currently seems to be beyond dispute, is homocysteine. The purpose of this article is to evaluate the concentration of homocysteine in children and youth with Type 1 diabetes, and to attempt to determine the dependence between homocysteine and the degree of metabolic control, the duration of the illness, the age at onset, the insulin dose, the appearance of complications, and a family history of ischemic heart disease. MATERIAL AND METHODS: Our research involved 103 children and youth (average age 13.3 years) with Type 1 diabetes, with an average duration of illness of 5.3 years. The control group consisted of 44 healthy, non-obese children. The concentration of homocysteine was measured using the AXIS homocystein EIA immunoenzymatic method with a set of reagents from the Bio Rad company. RESULTS: The average homocysteine concentration in the experimental group was 5.6 micromol/L, which did not constitute a significant difference from the control group's 6.1 micromol/l. No statistically significant differences were discovered in the concentration of homocysteine depending on the degree of metabolic control, age at onset, method of insulinotherapy, or family history. A significant increase in the concentration of homocysteine was found in children who had been ill for a long time (more than 10 years): 6.1 micromol/L, as against 5.1 micromol/l in children who had been ill for a shorter period of time, and a significantly higher concentration of Hcy in children with diabetic complications (6.1 vs 5.3 micromol/L) and in children with arterial hypertension. CONCLUSIONS: The significant increase in the concentration of homocysteine in children with Type 1 diabetes and arterial hypertension indicates that this group is particularly exposed to early atherosclerotic changes, independently of metabolic control and the parameters of lipid metabolism, and requires the implementation of treatment aimed at reducing the blood concentration of homocysteine.

50: Forsch Komplementarmed Klass Naturheilkd 2000 Aug;7(4):208-12

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51: Clin Invest Med 2000 Aug;23(4):220-6

Elevation of plasma homocysteine levels associated with acute myocardial infarction.

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OBJECTIVE: To study the effect of acute myocardial infarction (AMI) on plasma homocystein (Hcy) levels, to determine the optimal time to measure this risk factor for coronary artery disease. DESIGN: A prospective case study. SETTING: The Division of Cardiac Sciences, Grey Nuns Hospital in Edmonton. PATIENTS: Sixty-two patients (40 men, 22 women) admitted to hospital with AMI. INTERVENTION: Measurement of Hcy levels within 48 to 72 hours of admission and at 6 weeks after discharge from the Coronary Care Unit. In a second group of 15 patients, the Hcy levels were measured on hospital days 1 and 3. MAIN OUTCOME MEASURE: Comparison of the Hcy levels measured at the time of AMI and after discharge. RESULTS: Mean (and standard error of the mean) Hcy level measured during the AMI (13.6 [0.98] micromol/L) was significantly higher ($p < 0.05$) than at 6 weeks (12.1 [1.01] micromol/L). Based on the 48- to 72-hour and 6-week determinations, 31 and 21 patients, respectively, had abnormal Hcy levels (greater than 12 micromol/L) ($p < 0.001$). In the separate group of 15 patients, the Hcy level measured on day 3 (9.7 [0.6] micromol/L) was noted to be significantly higher ($p < 0.01$) than on day 1 (7.7 [0.8] micromol/L). CONCLUSIONS: There is an elevation of Hcy during AMI that may be related to an increase in the acute-phase reactant proteins. Thus, Hcy measurement should be deferred for 6 weeks in order to determine the true baseline level.

52: Rev Port Cardiol 2000 May;19(5):581-5

[Prognosis significance of blood homocysteine after myocardial infarction]

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INTRODUCTION AND AIMS: Homocysteinemia is an independent risk factor of coronary artery disease and of myocardial infarction. In the present study we intend to relate fasting homocystein levels to prognosis after a myocardial infarction. METHODS: From 1990 to 1992, we studied fasting homocysteinemia levels on a group of 112 patients aged under 56 years that had suffered a myocardial infarction between 3 and 12 months before. We obtained, the patients names, addresses, phone numbers and physicians' name. Seven years later (on average) we collected data regarding the patients evolution, consulting medical records, their physicians or by personal contact. We evaluated complications, namely mortality, vascular morbidity, such as unstable angina, re-infarction, stroke, and the need for invasive procedures (catheterism, PTCA, CABG). According to previous studies of the group, we used a cut-point of 10.10 mumol/L to define

patients with normal or pathological levels of homocysteinemia. We excluded all patients that took vitamin B supplements, co-factors of HC metabolism, during this follow-up. RESULTS: We were able to obtain data on 110 patients. Patients with normal HC levels (n = 62) presented less global complications (26 versus 72%, p < 0.0001), non significant tendency to have lower mortality (1.6 versus 6%), had lower morbidity (14 versus 36%, p < 0.01) and lower invasive procedure need (18 versus 48%, p < 0.001). In the group with pathological homocystein levels (n = 48), those with higher homocystein levels presented a higher degree of complications. CONCLUSIONS: In this population with myocardial infarction under 56 years of age, a high homocysteinemia level is an important prognostic factor. This study suggests that we can improve the prognosis and decrease the complications after myocardial infarction by lowering elevated homocystein levels.

53: Presse Med 2000 Apr;29(13):737-41

[Homocysteinemia: role in vascular disease]

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HEREDITARY DISEASE: Hereditary anomalies of homocysteine metabolism are quite uncommon and manifest by very high homocysteine levels (> 100 mumol/l) and associated homocysteinuria. The risk of premature cardiovascular disease is high. Clinical, biological and epidemiological data accumulated since the 70 s have demonstrated that a moderately elevated serum homocysteine level favors the development of atherothrombosis. PROVEN RISK: The risk of coronary or cerebral events is 1.5 to 3-fold higher for fasting homocysteine levels above 15 mumol/l. These data show that moderately elevated homocysteine level is a powerful cardiovascular risk factor. Further information is however needed to ascertain its frequency in the population and determine whether it is a truly independent risk factor. THERAPEUTIC OPTIONS: Most cases of moderately elevated homocysteine can probably be explained by gene-environment interactions. Homocysteine levels can be lowered by oral administration of vitamin cofactors implicated in homocystein metabolisms: folic acid, vitamin B6, vitamin B12.

54: Rev Neurol 1999 Nov 1-15;29(9):836-47

[From the genetics to the prevention of stroke]

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Genetic risk factors implicated in stroke are reviewed. There is evidence that family history of vascular disease is an independent risk factor for stroke. Twin studies demonstrated that there is a genetic component for stroke. I review the possible pathogenetic relevance of several vascular risk factors, namely dyslipoproteinemia, Lp(a), ApoE, homocystein, and prothrombotic states. Finally, I carry out an overview of genetic monogenic disorders manifesting with embolic stroke, thrombotic stroke or hemorrhagic stroke. This review corroborates that there are many genetic risk factors

of stroke, though further studies will be necessary to establish whether or not these factors are pathogenetically independent from acquired factors.

55: Przegl Lek 1999;56(7-8):520-4

[Hyperhomocysteinemia in chronic renal failure]

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Cardiovascular disease constitute the main cause of death in chronic renal failure patients on maintenance dialysis. During the last years one of the suspected cause promoting atherosclerotic lesions in this group of patients has been increased plasma homocystein level. The following article presents selected causes of hyperhomocysteinemia in chronic renal failure patients, mechanism of their toxic effect on cardiovascular system and methods of treatment of these disturbances.

56: Tidsskr Nor Laegeforen 1999 Oct;119(24):3577-9

[Gastrointestinal disease with elevated plasma homocysteine level]

Coll, P, Guttormsen, A B, Berstad, A

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Elevated plasma homocystein (tHcy) is a marker for functional deficiency of folate and/or cobalamin. Malabsorption of these vitamins occurs in various gastroenterologic diseases. A frequent mutation (C677T) in the gene coding for the enzyme methyltetrahydrofolate reductase (MTHFR) is often associated with elevated values of tHcy. We have investigated 24 patients with tHcy > 40 mumol/l for gastrointestinal disease that can contribute to such elevation. Of these, 19 were homozygous for mutated MTHFR, four were heterozygous and one was normal. We found two cases of probable celiac disease, one case of Crohn's disease and one case of ulcerative colitis. These four were homozygous for the C667T mutation. Furthermore, we found eight persons who were anacidic; four homozygous, three heterozygous and one normal. All had gastritis histologically, six had serum gastrin > 50 pmol/l, and four were already on treatment with cobalamin injections. Helicobacter pylori-infection was found in nine out of 22 persons. Gastrointestinal disease occurs frequently in patients with tHcy > 40 mumol/l, but with the exception of conditions resulting in serious deficiency of cobalamin, these diseases alone do not seem sufficient to cause such high levels. We suggest that a reasonable approach to patients with homocystein values above 40 mumol/l is to exclude cobalamin deficiency, and that further investigations should be based upon thorough anamnesis and symptoms.

57: Cas Lek Cesk 1999 May;138(11):333-6

[Diagnostic significance of mild hyperhomocysteinemia in a population of children with parents or grandparents who have peripheral or coronary artery disease]

Hyánek, J, Stríbrný, J, Sebesta, P, Klika, M, Kramár, J, Kozich, V, Martiníková, V, Macháckova, L, Orendác, M, Loucka, M, Dubská, L, Pejznochová, H, Táborský, L, Cabrnochová, I

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BACKGROUND: A rise of the homocysteine plasma level--mild hyperhomocysteinaemia--is considered an independent risk factor for the development of vascular damage. It is due to hereditary deficiency of 5,10-methylene-tetrahydrofolate reductase with accentuation of vitamin deficiency (folic acid, vitamin B6 and B12). In previous studies the authors confirmed this fact in the population of patients with aortocoronary or peripheral arterial bypasses. The assumed autosomal recessive transmission of this deficiency should make it possible to detect carriers of this metabolic deviation already in childhood. By selective screening of the child population at risk it would thus be possible to detect affected subjects in time and prevent the development of vascular disease by preventive folate administration. METHODS AND RESULTS: In a group of 38 children and grandchildren from risk families where at least one of the parents or grandparents was operated on account of vascular obliterating disease the total homocysteine plasma level was examined by the chromatographic method. An increase of total homocystein (8.7 +/- 2.7 mumol/l) was found as compared with children from the non-risk population (5.4 +/- 1.8 mumol/l), ($p < 0.001$). The total homocysteine values however were dependent on the child's age and were more marked in children above 12 years of age. In the parental population mild hyperhomocysteinaemia was present in 38% of those with aortocoronary bypasses and in 43% of those with peripheral arterial bypasses. CONCLUSIONS: The authors found significantly elevated total homocysteine levels in the child population from risk families with obliterating vascular disease. The total homocysteine level depends on the child's age and is more markedly expressed in children above 12 years of age.

59: Rev Port Cardiol 1999 Feb;18(2):155-9

[The effect of sex and menopause on basal blood levels of homocysteine and after methionine loading]

Reis, R P, Azinheira, J, Reis, H P, Pina, J E, Correia, J M, Luís, A S

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INTRODUCTION AND OBJECTIVES: We have already proved that basal and after load homocysteinemia are risk factors for vascular disease and it is also known that premenopausal women are relatively protected against this disease. The objective of this paper was the assess whether there are any differences in the plasma levels of homocystein which might contribute to explain the differences in the incidence of vascular diseases found in both sexes. PATIENTS AND METHODS: Two hundred and four patients (153 males) without previous vascular disease were enrolled in the study. These patients were participating in a screening program for cardiovascular risk factors in a central hospital in Lisbon. We evaluated the basal homocysteinemia and homocysteinemia 6 hours after an oral load with

methionine (0.1 g/kg body weight). Basal and after load homocysteinemia in men and women, as well as in women before and after menopause, was compared. Because homocysteinemia does not have a normal distribution, we used non-parametric statistical tests, namely the Mann-Whitney test. RESULTS: Men had higher values for basal homocysteinemia than women (mean and standard deviation)--9.64 +/- 3.15 versus 8.56 +/- 2.82 mumol/l, (p = 0.0018)--as well as for after load homocysteinemia--24.40 +/- 7.84 versus 23.71 +/- 10.16 mumol/L, non significant difference. Premenopausal women (n = 42) had lower basal homocysteinemia values than post menopausal women (n = 9)--8.41 +/- 3.02 versus 9.23 +/- 1.38 mumol/L, p < 0.05--and similarly after load homocysteinemia values--23.86 +/- 10.65 versus 23.01 +/- 7.47 mumol/L. CONCLUSIONS: Basal homocysteinemia is significantly higher in men than in women. After menopause, basal homocysteinemia levels increase significantly in women, approaching those in men. The levels of after load homocystein are not dependent on sex or pre- or postmenopausal condition. Homocysteinemia might explain, at least partly, the differences in the incidence of vascular disease in both sexes and the increased vascular risk in postmenopausal women.

60: Nippon Rinsho 1998 Oct;56(10):2675-80

[Risk factors and prevention of acute coronary syndrome]

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Acute coronary syndromes (ACS) such as unstable angina, myocardial infarction, or sudden ischemic death evolve from coronary thrombosis consequence of atherosclerotic plaque disruption. Plaque stabilization is an important therapeutic strategy in the prevention of ACS. Coronary risk factors include age, male sex, cigarette smoking, hypertension, dislipidemia, diabetes mellitus, insulin resistance and/or hyper insulinemia, obesity, sedentary lifestyle, stress, and the morning surge of sympathetic activity. New risk factors are emerging such as high homocystein, inflammation, and some kinds of infection. Control of blood pressure and cholesterol clearly reduce the risk of coronary events and mortality although the effects of antihypertensive therapy have been less than expected. The benefits of smoking cessation, moderate alcohol consumption, low-dose aspirin prophylaxis, estrogen-replacement therapy in postmenoposal women have also been shown.

61: Ann Biol Clin (Paris) 1998 Jan-Feb;56(1):49-56

[Evaluation of hemostasis in venous thromboembolism pathology]

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Thromboembolic disease results from an hypercoagulable state and multifactorial causes may lead to hypercoagulability. Thrombogenic risk factors can be acquired and/or inherited. For each thrombophilic patient, the main clinical features retained are: the patient age, the familial history, the recurrence of thromboembolic events, an unusual site of thrombosis. Anti-phospholipid antibodies, which are considered as acquired

thrombogenic risk factors, can be detected with coagulation tests and/or Elisa methods. The association of antiphospholipid antibodies with thrombosis is defined as the anti-phospholipid syndrome. Last decades, genetic risk factors were identified. First of all, antithrombin, protein C and protein S deficiencies were described. These deficiencies are involved in about 10% of patients who develop thrombosis before the age of 50. In 1993, a new genetic risk factor was discovered: activated protein C resistance which is due to the Q506 mutation in factor V. This defect represents the most prevalent abnormality of inherited thrombophilia, affecting 20 to 40% of thrombophilic patients. Interestingly, hyperhomocysteinemia, known as potentially predisposing to arterial disease, was also recognized as a risk factor for venous occlusive disease. Several genes encoding homocystein metabolism enzymes, such as cystathionine beta-synthase or methylenetetrahydrofolate reductase are concerned. Establishment of a causal association between the presence of a biological abnormality and the occurrence of thrombosis may lead to an adapted prophylaxis whatever the risk situation.

62: Tidsskr Nor Laegeforen 1998 Jun;118(15):2370-4

[Molecular biology in the diagnosis of cardiovascular diseases]

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Genes shown to affect risk factors or protective factors with respect to coronary heart disease (CHD) have been identified at the APOB, APOAI, LPA, LDLR, APOE and CETP loci. Rare mutations (e.g., in the LDLR and APOE genes) may have a major effect, whereas genes belonging to normal polymorphism have only a moderate effect. Even genes with only a slight effect can be clinically important in combination with other genes or life-style factors. There is gene to gene interaction between LDLR and APOE genes. Important risk factors determined by genes as well as by environmental factors are homocystein and fibrinogen. In addition to traditional lipid and apoprotein measurements, the levels of Lp(a) lipoprotein, fibrinogen and homocystein should be examined in connection with diagnosing CHD cases. DNA analyses are appropriate when familial hypercholesterolemia is suspected, and it is likely that the importance of mutation analyses will increase significantly in the near future.

63: Herz 1998 May;23(3):153-62

[Arteriosclerosis and coronary heart disease--strengths and weaknesses in the classical risk factor concept]

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Several cardiovascular risk factors were identified (high LDL-cholesterol, low HDL-cholesterol, homocystein, Lp(a), and many others). Hypercholesterolemia has been shown to be one of the most important cardiovascular risk factors in man. Interventional studies for primary and secondary prevention demonstrate a beneficial effect of cholesterol lowering therapy. However, numerous CAD-patients suffer a second coronary

event despite the appropriate lipid-lowering treatment. Furthermore moderate hypercholesterolemia has only poor predictive power indicating an upcoming myocardial infarction. Therefore we need additional research in CAD prevention and in identifying so far unknown or unconsidered CAD risk factors.

64: Arch Mal Coeur Vaiss 1996 Oct;89(10):1241-6

[Hyperhomocysteinemia in coronary artery diseases. Apropos of a study on 102 patients]

Blacher, J, Montalescot, G, Ankri, A, Chadefaux-Vekemans, B, Benzidia, R, Grosgogeat, Y, Kamoun, P, Thomas, D

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Homocystein is at the crossroads of the metabolic pathways of sulphuric amino acids. Homocystinuria is a congenital autosomal recessive disease, usually related to cystathionine beta-synthetase deficiency. Children with homozygotic forms of the disease have early vascular complications which represent the main cause of death. Moderately elevated serum homocystein levels are related to two major genetic factors (heterozygotic cystathionine beta-synthetase deficiency and mutation of the 5-10 methylene tetrahydrofolate reductase) and several minor, genetic and non-genetic factors (folic acid, vitamins B6 and B12 and betain deficiencies). Previous studies have suggested that hyperhomocysteinaemia could be a cardiovascular risk factor. This study was based on 222 subjects including 102 consecutive patients with angiographically documented coronary artery disease and 120 control subjects without vascular disease. No relationship was observed between serum homocystein concentrations and the classical cardiovascular risk factors. Coronary patients had higher average homocystein concentrations than control subjects (11.27 +/- 0.52 vs 8.77 +/- 0.31 mumol/l); $p < 0.0001$): moreover, the prevalence of hyperhomocysteinaemia (> 15.67 mumol/l) was higher in the coronary group (15.7%) than in the controls (2.5%). A significant relationship was also observed between homocystein concentrations and the severity of the coronary disease (defined by a coronary score) and the number of diseased vascular territories. These results underline the relationship between homocystein and vascular risk, especially that of coronary artery disease. The treatment of hyperhomocysteinaemia by folic acid supplements is effective in correcting plasma levels, without side effects and at a relatively low cost.

65: Presse Med 1996 Mar;25(11):531-6

[Value of an extensive biological study in venous or arterial thromboses]

Tazi, Z, Cacoub, P, Koskas, F, Chabanel, A, Chadefaux-Vekemans, B, Horellou, M H, Viard, J P, Piette, J C, Kieffer, E, Godeau, P

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OBJECTIVES: The aim of this work is to study the signification of an extensive biological evaluation in patients with "unexplained" thrombosis. We studied 78 patients with more than one arterial and/or venous thromboembolic event. METHODS: Fifty-four patients were admitted for unexplained deep venous thrombosis (group I, n = 19, 9 men and 10 women)

and/or arterial thrombosis (group II, n = 35, 21 men and 14 women). A third group (group III) included 24 patients (13 men, 11 women) known to have a pathologic state which can lead to a thrombotic event. RESULTS: The patients in both groups I and II had, more often than normal subjects, a high level of homocysteinemia (26% vs 3%, p < 0.001), anti-beta 2 glycoprotein 1 (18.5% vs 3%, p < 0.001) and antiphospholipid antibodies (13% vs 3%, p < 0.02). We also found a significant association between an increase of erythrocytic aggregation and arterial thrombosis (group II). In the third group, for both arterial (n = 14) and venous (n = 10) thrombosis, we found a high level of anticardiolipin antibodies (25% vs 3%, p < 0.001), anti-beta 2 glycoprotein 1 antibodies (12.5% vs 3%, p < 0.05) and abnormal erythrocytic aggregation (16.5% vs 3%, p < 0.01). In these 3 groups the other studied parameters (Lp(a), platelet aggregation, cryoglobulin, cryofibrinogen, antinuclear antibodies, anticytoplasm antibodies, plasma and urine immunoelectrophoresis, protein C, protein S, antithrombin III, plasminogen) were not different from levels observed in normal subjects. CONCLUSION: An extensive biological analysis, including plasma homocystein level, anticardiolipin antibodies, anti-beta 2 glycoprotein 1 antibodies and a study of the erythrocytic aggregation would appear to be of value in patients presenting recurrent arterial or venous thromboembolic events. Specific therapy can be applied in case of abnormal results continued anticoagulant therapy for anticardiolipin and anti-beta 2 glycoprotein 1 antibodies, and a vitamin therapy for increased homocysteinemia.

66: Clin Exp Rheumatol 1993 Mar-Apr;11 Suppl 8:S101-5

Antifolates in rheumatoid arthritis: a hypothetical mechanism of action.

Baggott, J E, Morgan, S L, Ha, T S, Alarcón, G S, Koopman, W J, Krumdieck, C L

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The antifolates, methotrexate, aminopterin, 10-deazaaminopterin and sulfasalazine are clinically useful in the treatment of rheumatoid arthritis. Toxicity, rather than efficacy, appears to the the major factor limiting the usefulness of the classical antifolates (i.e., methotrexate and 10-deazaaminopterin). The fact that folate supplementation of methotrexate-treated rheumatoid arthritis patients reduces toxicity without altering efficacy also suggests that inhibition of the drug's target enzyme, dihydrofolate reductase, is not complete and not essential for efficacy. Since polyglutamates of methotrexate are direct inhibitors of thymidylate synthase and folate dependent enzymes of purine biosynthesis, the efficacy of this agent may involve blockade of these pathways. We hypothesize that blockage of aminoimidazole carboxamide ribotide transformylase, the folate dependent enzyme responsible for the insertion of carbon 2 into the purine ring, produces an immunosuppression mediated by secondary inhibition of adenosine deaminase, and S-adenosyl homocystein hydrolase by aminoimidazolecarboxamide metabolites. This mechanism of immunosuppression may explain the clinical effect of methotrexate, 10-deazaaminopterin, and possibly sulfasalazine. Since purine biosynthesis is a fundamental process, blockading this pathway may also decrease leukotriene production and interleukin-1 expression, which also could contribute to the efficacy of methotrexate.

67: J Pharm Belg 1991 Jul-Aug;46(4):271-80

[The nutritional importance and pharmacologic effects of cobalt and vitamin B 12 in man]

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Cobalt is an unique trace element for man as it can only reveal its essential properties if provided directly as its biological active form, cobalamin or vitamin B12, the daily requirement of which is 1 to 2 micrograms in adults. This vitamin takes part in the activity of the enzyme methylmalonyl coenzyme A mutase, involved in the conversion of propionyl CoA to succinyl CoA, an intermediary product of the citrate cycle, and of the 5-methyltetrahydrofolate: homocystein methyltransferase, working in the metabolism of methionin and in DNA synthesis. Vitamin B12 deficiency is responsible for a megaloblastic anemia called pernicious anemia and for specific neurological disorders that can be corrected by adequate supplementation. Inorganic cobalt salts can therefore not be considered as essential micronutrients for man, but being able to induce polycythemia, they have a pharmacological property that was recommended in the treatment of various anemias, and they are also used in the management of cyanide poisoning.

68: J Med Chem 1987 Sep;30(9):1599-603

Isozyme-specific enzyme inhibitors. 14. 5'(R)-C-[(L-homocystein-S-yl)methyl]adenosine 5'-(beta,gamma-imidotriphosphate), a potent inhibitor of rat methionine adenosyltransferases.

Kappler, F, Vrudhula, V M, Hampton, A

The title compound is a covalent adduct of L-methionine (Met) and beta,gamma-imido-ATP. In its synthesis the N-Boc derivative of 5'(R)-C-(aminomethyl)-N6-benzoyl-5'-O-tosyl-2',3'-O- isopropylidenadenosine was converted by the successive actions of CF3CO2H and HNO2 into the corresponding 5'(R)-C-hydroxymethyl derivative. Treatment of this with disodium L-homocysteinate led to attack of sulfur at C6', apparently via a 5',6'-epoxide, and to total stereoselective inversion at C5' to furnish, after debenzoylation, 5'(R)-C-(L-homocystein-S-ylmethyl)-2',3'-O-isopropylidene ade nosine. The 5' configuration was established by conversion of this into the known 5'(S)-C-methyl-2',3'-O-isopropylidene adenosine with Raney nickel. The alpha-amino acid residue was protected as an N-Boc methyl ester, after which the 5'-hydroxyl was phosphorylated with benzyl phosphate and dicyclohexylcarbodiimide. The phosphoanhydride bond with inorganic imidodiphosphate was then created by established methods. Finally, blocking groups were removed under conditions that gave the desired adduct with no racemization of its L-methionine residue. It was a potent inhibitor [KM(ATP)/Ki = 1080; KM(Met)/Ki = 7.7] of the M-2 (normal tissue) form of rat methionine adenosyltransferase and of the M-T (hepatoma tissue) form [KM(ATP)/Ki = 670; KM(Met)/Ki = 22]. Inhibitions were competitive with respect to ATP or to L-methionine, indicating a dual substrate site mode of binding to the enzyme forms.

69: Chem Biol Interact 1987;64(1-2):181-92

The binding of an aminoazo dye carcinogen to a specific methionine residue in rat liver alcohol dehydrogenase in vivo.

Coles, B, Beale, D, Miller, D, Lay, J, Kadlubar, F, Aitken, A, Ketterer, B

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On the administration of 3'-methyl-N,N-dimethyl-4-aminoazobenzene to rats pure aminoazo dye-bound alcohol dehydrogenase accounting for 45% of the total soluble protein bound aminoazo dye is isolated from the liver soluble supernatant. Tryptic digestion of that purified aminoazo dye-bound enzyme yields an aminoazo dye-bound nonapeptide which has a sequence identical to amino acids 301-309 in the known sequence of alcohol dehydrogenase (H. Jornvall and O. Markovic, Eur. J. Biochem., 29 (1972) 167-174) with the exception of methionine 306 which is replaced by an aminoazo dye modified amino acid. The nature of the aminoazo dye adduct was determined by studying the structure of the related tetrapeptide obtained by Pronase B digestion and shown by proton NMR spectroscopy and fast atom bombardment mass spectroscopy to have the structure 3-(Val. Asn. Pro. Homocystein-S-yl)-4-methylamino-3'-methylazobenzene. This carcinogen-protein adduct is assumed to arise from attack of the ultimate carcinogenic metabolite, N-sulphonyloxy-4-methylamino-3'-methylazobenzene (FF. Kadlubar, J.A. Miller and E.C. Miller, Cancer Res., 36 (1976) 2350-2359) at the sulphur of methionine 306 followed by spontaneous S-demethylation. This highly specific reaction of carcinogen with alcohol dehydrogenase lowers its Vmax and increases its Km with cyclohexanone thereby reducing its catalytic efficiency for this substrate. This highly specific reaction of the carcinogen with alcohol dehydrogenase may be regarded as a major detoxication reaction.

70: J Steroid Biochem 1983 Jul;19(1B):639-44

Possible mechanism of action of 2-hydroxylated estradiol on the positive feedback control for LH release in the rat.

Ladosky, W, Azambuja, H M, Schneider, H T

Evidence was given to support a positive role of 2-hydroxyestradiol on the LH surge. The catecholestrogen may act by its catechol A ring on the nucleus arcuatus COMT, consequently leaving the noradrenaline free. The result may be a longer action on the peptidergic terminal in the median eminence and an increase in the LH secretion by the pituitary. This assumption is supported by the observations that the catecholestrogen effect can be mimicked by homocystein, an aminoacid able also to inhibit COMT activity, having neither a steroid nor a catechol structure. The fact that alpha-MIT is able to prevent homocystein-induced increase in LH suggests that it is acting by protecting the local increase of the catecholamine. After ten years of intensive effort to understand the possible physiological role of the catecholestrogens, attention was mostly paid to its structural similarity to estrogen and a great deal of effort was made to understand its function by acting upon the estrogen receptor in the cytosol. The evidence for catecholestrogen action upon COMT, an outside membrane enzyme involved in the process of catecholamine degradation, supports the idea of a catechol action for 2-OHE2. The present evidence strongly supports the physiological importance of the catechol group in the 2-OHE2 in its action mechanism. However, a true physiological role for the catecholestrogens remains to be solved. The evidence we bring confirms once more that catecholestrogens may have a function and explains a new mechanism of action. However, the basic question concerning the true amount of catecholestrogen existing in the hypothalamic nuclei, either brought by

the blood stream or locally produced, still needs to be solved: we cannot say whether the mechanism we described is a functioning one, whether it is just brought about by the experimental increase of the catecholestrogen or the artificial blockage of COMT.

71: Haematol Blood Transfus 1981;26:197-203

Episomal and nonepisomal herpesvirus DNA in lymphoid tumor cell lines.

Kaschka-Dierich, C, Bauer, I, Fleckenstein, B, Desrosiers, R C

Tumor cell lines derived from Herpesvirus saimiri (H. saimiri)- and Herpesvirus ateles (H. ateles)-induced lymphomas of New World primates and rabbits contain multiple copies of viral genomes. Partial denaturation mapping and blot hybridizations of episomal DNA from lymphoid tumor cell line No. 1670 showed that a 12.5md-fragment is missing which represents the EcoRI D- and H-fragments of virion L-DNA. However, the missing piece can be demonstrated in total cellular DNA by reassociation kinetics, possibly because it persists in integrated form. Both episomal and nonepisomal H-DNA are heavily methylated in a number of the lymphoid cell lines, and methylation may be reduced by conventional methylation inhibitors (S-adenosyl homocystein, SIBA) as well as by the tumor promoting phorbol ester TPA.

72: J Biol Chem 1980 Nov;255(22):10822-7

S-Adenosylmethionine and S-adenosylhomocystein metabolism in isolated rat liver. Effects of L-methionine, L-homocystein, and adenosine.

Hoffman, D R, Marion, D W, Cornatzer, W E, Duerre, J A

The effects of varying concentrations of L-methionine, L-homocysteine, and adenosine on the tissue levels of S-adenosylmethionine (AdoMet) and S-adenosyl-homocystein (AdoHcy) were investigated in perfused liver. In the normal liver, the intracellular concentration of AdoMet was dependent upon the availability of methionine. In the presence of high concentrations of methionine the maximum level of AdoMet attainable was 300 nmol/g of liver. The exogenous concentration of methionine did not alter the hepatic concentration of AdoHcy (8 to 20 nmol/g) while adenosine or homocysteine blocked hydrolysis of AdoHcy resulting in elevated levels of AdoHcy (400 to 600 nmol/g) and AdoMet (300 to 600 nmol/g). The addition of both adenosine (4mM) and homocysteine (3.4 mM) to the perfusate further increased the levels of AdoHcy (4 mumol/g) and AdoMet (1.2 mumol/g). As the concentration of AdoHcy increased, significant amounts of this compound were released into the perfusate, while AdoMet was not detected. Under all conditions where AdoHcy accumulated in the cell, a concomitant increase in the AdoMet level occurred. Apparently AdoHcy acts as a positive effector of the S-adenosylmethionine synthase. The hepatocytes did not take up significant amounts of [methyl-14C]AdoMet from the perfusate nor were any [14C]methyl groups from this compound incorporated into histones, DNA, or phospholipids. In contrast, [14C]methyl groups were readily incorporated into these macromolecules from exogenous [methyl-14C]methionine. The addition of adenosine (4 mM) and homocystein (3.4 mM) shifted the AdoMet:AdoHcy ratio from 8.2 to 0.3. Under these conditions, transmethylation was inhibited markedly.

73: J Bacteriol 1980 Jul;143(1):427-31

Inhibition of leucine transport in Saccharomyces by S-adenosylmethionine.

Law, R E, Ferro, A J

S-Adenoxyl-L-methionine (SAM) inhibited leucine transport in Saccharomyces cerevisiae. By using a mutant defective in the active transport of SAM, we demonstrated that the inhibitory effect was exerted at an extracellular site. Cells preincubated wtih SAM for 120 min became refractory to its inhibitory effect, which was not a result of either the active transport or the metabolism of SAM. The quantitative recovery of labeled SAM from the incubation medium indicated that SAM, and not a metabolite, was the true inhibitory molecule. S-Adenosyl-L-homocysteine and S-adenosyl-L-ethionine also functioned as inhibitors of leucine transport, whereas S-adenosyl-D-methionine, S-adenosyl-D-homocystein, 5'-methylthioadenosine, 5'-dimethylthioadenosine, and adenosine lacked this property. Kinetic studies demonstrated that SAM was a competitive inhibitor of leucine transport.

74: Proc Natl Acad Sci U S A 1980 Jul;77(7):4292-6

Resistance of an adenosine kinase-deficient human lymphoblastoid cell line to effects of deoxyadenosine on growth, S-adenosylhomocysteine hydrolase inactivation, and dATP accumulation.

Hershfield, M S, Kredich, N M

Accumulation of dATP derived from 2'-deoxyadenosine (dAdo), causing inhibition of ribonucleotide reductase and depletion of the other deoxynucleotide substrates required for DNA synthesis, has been suggested as the cause of the lymphopenia and immune defect in inheritable deficiency of adenosine deaminase (adenosine aminohydrolase, EC 3.5.4.4). dAdo also inactivates the enzyme S-adenosylhomocysteine hydrolase (AdoHcyase; S-adenosyl-L-homocystein hydrolase EC 3.3.1.1) which is involved in the catabolism of S-adenosyl-L-homocysteine (AdoHcy), both a product and a potent inhibitor of S-adenosylmethionine-dependent transmethylation. We have tried to determine whether inactivation of AdoHcyase might also contribute to dAdo toxicity to adenosine deaminase-inhibited cells. dAdo rapidly inactivates intracellular AdoHcyase and causes the accumulation of AdoHcy in WI-L2 human B lymphoblastoid cells. Low concentrations of adenosine (Ado), which block binding of dAdo to purified AdoHcyase, prevented inactivation of intracellular AdoHcyase and also lessened the growth-inhibitory effect of dAdo. A mutant of this cell line which lacks Ado kinase and accumulated endogenously synthesized Ado was resistant to the effects of dAdo on both growth and AdoHcyase activity. The mutant also accumulated far less dATP from dAdo than did its parent and was resistant to the inhibitory effect of dAdo on DNA synthesis, indicating the Ado kinase is involved in dAdo phosphorylation in these cells. Combinations of deoxycytidine, thymidine, and deoxyguanosine that could prevent dATP-mediated depletion of deoxynucleotide pools but not AdoHcyase inactivation were less effective than Ado in preventing dAdo toxicity to normal lymphoblasts. Our results suggest that inactivation of AdoHcyase, as well as dATP accumulation, contributes to dAdo toxicity.

75: Biochem J 1978 Mar;170(3):627-30

Maintenance of glutathione content is isolated hepatocyctes.

Viña, J, Hems, R, Krebs, H A

1. During the standard procedure for the preparation of rat hepatocytes, about half of the cellular GSH (reduced glutathione) is lost. 2. This loss is prevented by the addition of 0.1 mM-EGTA (but no EDTA) to the perfusion medium. 3. On incubation with and without EGTA, isolated hepatocytes prepared in the presence of EGTA lose GSH. This loss is prevented by near-physiological concentrations of methionine or homocysteine, but not of cysteine. 4. Cysteine, at concentrations above 0.2 mM, causes a loss of GSH probably by non-enzymic formation of a mixed disulphide. 5. Serine together with methionine or homocystein increases GSH above the value in cells from starved rats in vivo. This is taken to suggest that cystathionine may be a cysteine donor in the synthesis of gamma-glutamylcysteine, the precursor of GSH.

77: Strahlentherapie 1976 Apr;151(4):311-7

[Radio-chemotherapy of cervix carcinoma. I. Clinical part]

Paeschke, K D

A prospective study was performed for a new model concerning the potentiation of radiation with Podophyllum (Proresid) and the radioprotection with Acethylhomocystein-thiolactone (Reducdyn) in cases of the squamous cell carcinoma of the uterine cervix. The study was carried out on the basis of alternated data of birth. The total number of the randomization was 256, consisting of 173 stages II und 83 stages III. All patients were irradiated with 6000 mgeh Ra and 4500 R 60Co. In addition to the irradiation one group of 128 patients received an infusion of 1g Podophyllum/day after irradiation. Another group of 46 patients was treated prior to irradiation with 1g Acethyl-homocystein-thiolactone (AHCT) and with Podophyllum after exposure. The total dosage was between 30 and 50g Pod. and 30 and 50g AHCT. It could be shown that the survival rate after three years was increased up to 15%. An earlier study revealed a five-year-survival rate of 23%.

78: J Clin Invest 1975 Nov;56(5):1293-1301

Studies on N5-methyltetrahydrofolate-homocystein methyltransferase in normal and leukemia leukocytes.

Peytremann, R, Thorndike, J, Beck, W S

A cobalamin-dependent N5-methyltetra-hydrofolate-homocysteine methyltransferase (methyl-transferase) was demonstrated in unfractioned extracts of human normal and leukemia leukocytes. Activity was substantially reduced in the absence of an added cobalamin derivative. Presumably, this residual activity reflects the endogeneous level of holoenzyme. Enzyme activity was notably higher in lymphoid cells than in myeloid cells. Thus, mean specific activities (+/-SD) were: chronic lymphocytic leukemia lymphocytes, 2.15+/-1.16; normal lymphocytes, 0.91+/-0.59; normal mature granulocytes, 0.15+/-0.10; chronic myelocytic leukemia

granulocytes, barely detectable activity. Properties of leukocytes enzymes resembled those of methyltransferases previously studied in bacteria and other animal cells. Granulocytes and chronic myelocytic leukemia cells contain a factor or factors that inhibits Escherichia coli enzyme. The data suggest that the prominence of this cobalamin-dependent enzyme in lymphocytes and other mononuclear cell types may be related to their potential for cell division.

79: Biochim Biophys Acta 1975 Oct;403(2):301-14

Purification and properties of S-adenosyl-L-methionine: caffeic acid O-methyltransferase from leaves of spinach beet (Beta vulgaris L).

Poulton, J E, Butt, V S

1. An enzyme catalysing the methylation of caffeic acid to ferulic acid, using S-adenosyl-L-methionine as methyl donor, has been extracted from leaves of spinach beet and purified 75-fold to obtain a stable preparation. 2. The enzyme showed optimum activity at pH 6.5, and did not require the addition of Mg2+ for maximum activity. 3. It was most active with caffeic acid, but showed some activity with catechol, protocatechuic acid and 3,4-dihydroxybenzaldehyde. The Km for caffeic acid was 68 muM. 4. 4. The Km for S-adenosyl-L-methionine was 12.5 muM. S-Adenosyl-L-homocystein (Ki = 4.4 muM) was a competitive inhibitor of S-adenosyl-L-methionine. 5. The synthesis of S-adenosyl-L-homocysteine from adenosine and L-homocysteine and its consequent effect on caffeic acid methylation were demonstrated with a partially-purified preparation from spinach-beet leaves, which possessed both S-adenosyl-L-homocysteine hydrolase (EC 3.3.1.1) and adenosine nucleosidase (EC 3.2.2.7) activities. This preparation was also able to catalyse the rapid breakdown of S-adenosyl-L-homocysteine to adenosine and adenine; the possible significance of this reaction in relieving the inhibition of caffeic acid methylation by S-adenosyl-L-homocystein is discussed.

80: In Vitro 1975 Jan-Feb;11(1):14-9

Effect of methionine replacement by homocystine in cultures containing both malignant rat breast carcinosarcoma (Walker-256) cells and normal adult rat liver fibroblasts.

Halpern, B C, Ezzell, R, Hardy, D N, Clark, B R, Ashe, H, Halpern, R M, Smith, R A

When malignant W-256 rat breast carcinosarcoma cells are mixed with an equal number of normal adult rat liver fibroblasts and allowed to grow in a medium containing sufficient L-methionine and an excess of vitamin B12 and of folic acid, the malignant cells outgrow the normal cells, and within 2 weeks the tissue culture flasks contain only neoplastic cells. However, when ample DL-homocystine or homocysteine replaces methionine in the medium containing the same amount of vitamin B12 and folic acid, and seeded with the same type and number of malignant and normal cells, the malignant cells die and the normal cells thrive. Substantiating this conclusion are the results of injections into rats of comparable numbers of cells from each group after 3 weeks of growth in tissue culture. Fatal malignancies are produced by the homocystein-cultivated cells.