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***Barišić N, Schmidt C, Sidorova OP, Herczegfalvi A, Gekht BM, Song IH, et al. Congenital myasthenic syndrome (CMS) in three European kinships due to a novel splice mutation (IVS7 - 2 A/G) in the epsilon acetylcholine receptor (AChR) subunit gene*. Neuropediatrics 2002;33:249-54.**

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Mutations in the epsilon-acetylcholine receptor (AChR-epsilon) subunit gene cause congenital myasthenic syndromes (CMS) with postsynaptic neural transmission defects. The authors present 3 male and 2 female patients from three unrelated Croatian, Hungarian, and Russian families with autosomal recessive CMS. All patients manifested with variable degrees of ophthalmoparesis and generalized, fatiguable muscle weakness since birth or early infancy. Electrophysiological studies showed a decremental response in all patients indicating a neuromuscular transmission defect. Pyridostigmine treatment improved the proximal muscle weakness whereas the ophthalmoparesis remained unchanged in all patients. Analysis of the AChR-epsilon subunit gene showed homozygosity for a novel splice site mutation of intron 7 epsilon(IVS7-2A/G) in the two Croatian siblings. Epsilon-mRNA analysis by RT-PCR and direct sequencing revealed that exon 7 was spliced directly to exon 9 with skipping of exon 8. The Hungarian and Russian patients were heteroallelic carriers of the same mutation epsilon(IVS7-2A/G) and of a frameshifting mutation epsilon70insG and epsilon1293insG, respectively. The authors hypothesize that altered splice products may not be expressed as functional receptors at the cell surface. A haplotype analysis with polymorphic markers revealed a high degree of similarity for the epsilon(IVS7-2A/G) carrying allele in all families and may therefore indicate a common origin of the mutation.

Ćulić V, Eterović D, Mirić D, Silić N. Symptom presentation of acute myocardial infarction: influence of sex, age, and risk factors. Am Heart J 2002;144:1012-7.

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The purpose of this study was to examine the symptomatology of onset of acute myocardial infarction (AMI) in patients according to sex, age, and existence of conventional risk factors. This was a prospective, observational study of a large number of symptoms in 1996 patients admitted to Clinical Hospital Split between January 1990 and July 1995 as the result of a first AMI. For each patient, the structured data form covering experience of pain at 10 body locations and 11 other symptoms, baseline characteristics, risk factors, and peak cardiac enzyme levels was completed a median of 3 days after AMI. Any pain, and specifically chest pain, was more often reported by male patients, smokers, hypertensive patients, nondiabetic patients, and hypercholesterolemic patients. Women were more likely to report nonchest pain other than epigastric and right shoulder pain, as well as various nonpain symptoms. The independent predictors of atypical AMI presentation (ie, absence of pain) in both men and women were lower levels of creatine kinase-MB fraction ($p < 0.0001$ and $p = 0.0003$, respectively), diabetes mellitus ($p = 0.0002$ and $p = 0.002$, respectively), older age ($p = 0.001$ and $p = 0.01$, respectively), and absence of smoking in men ($p = 0.0005$). The independent predictors of presence of nonpain symptoms in both men and women were higher levels of creatine kinase-MB fraction ($p = 0.01$ and $p = 0.049$, respectively) and diabetes mellitus ($p = 0.048$ and $p = 0.005$, respectively); in men, it was hypercholesterolemia ($p = 0.01$). The results suggest that sex, age, smoking, hypertension, diabetes, and hypercholesterolemia may affect the symptoms in AMI. Women with diabetes represent a high-risk subgroup for painless onset followed by various other symptoms.

Ljubojević S, Lipozenčić J, Brenner S, Budimčić D. Pemphigus vulgaris: a review of treatment over a 19-year period. J Eur Acad Dermatol Venereol 2002;16:599-603.

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The authors present a retrospective analysis of 159 patients with pemphigus vulgaris and pemphigus vegetans who were admitted to the Department of Dermatology and Venereology, Zagreb University Hospital Center (Zagreb, Croatia) from 1980 to 1998. Female to male ratio was approximately 2:1. The mean age was 53 years. During the war years in Croatia (1991-95) the authors noticed a low incidence of pemphigus vulgaris, and from 1996 to 1998 the incidence almost doubled. Diagnosis was based on histopathology (showing typical pemphigus vulgaris changes in 156 or 98% patients), indirect immunofluorescence (positive in 122 or 77% patients), direct immunofluorescence (positive in 141 or 89% patients), and blister smear cytology (Tzanck test) (positive in 115 or 72% patients). High dosages of prednisone (100-150 mg) were given to 129 patients, which was combined with azathioprine. Patients with refractory pemphigus vulgaris were treated with intramuscular gold (14 patients) and plasmapheresis (five patients). All patients were treated with local ointments. The prolonged use of high doses of corticosteroids and immunosuppressants caused several complications, in particular, steroid diabetes (37 patients), skin infections (26 patients), arterial hypertension (23 patients), cardiorespiratory diseases (22 patients), sepsis (nine patients), etc. During the hospital treatment, 14 patients died, 10 during 1980-89 and only four during the 1990-98 period. The main causes of death were cardiorespiratory failure (six patients) and sepsis (five patients). Although pemphigus vulgaris is still a life-threatening disease, today it can be successfully treated with a combination of immunosuppressive agents. Early diagnosis and treatment of pemphigus vulgaris allow a better prognosis with lower mortality rates.

Vince A, Kutela N, Iščić-Bes J, Harni V, Ivanišević M, Sonicki Z, et al. Clinical utility of molecular detection of human papillomavirus in cervical samples by hybrid capture technology. J Clin Virol 2002;25(Suppl 3):109-12.

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High-risk human papillomaviruses (HPVs) are the primary risk factor for developing cervical carcinoma. Hybrid capture II

HPV Test (HCII) is a standardized test for molecular detection of HPV DNA in cervical swabs. The aim of the study was to evaluate the clinical utility of the HCII when used in combination with conventional cytology in a group of 171 women who were followed-up with both, cytology and molecular testing for 3 years. At the end of the study, only women positive for high-risk HPV at baseline had retained or worsened cervical intraepithelial neoplasia (CIN). In most women who were negative for high-risk HPV, CIN had resolved within 3 years. These results are in concordance with earlier studies reporting the highly negative predictive value of high-risk HPV testing. Both cytology and high-risk HPV testing provide significant clinical information on the current cervical status of a woman. They should be used in combination for primary screening of CIN, which will provide a more selective and cost-effective follow-up.

Bognar SK, Furač I, Kubat M, Čosović C, Demarin V. Croatian population data for arylsulfatase A pseudodeficiency-associated mutations in healthy subjects, and in patients with Alzheimer-type dementia and Down syndrome. Arch Med Res 2002;33:473-7.

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Arylsulfatase A (ASA) is a lysosomal enzyme involved in catabolism of cerebroside sulfate, whose deficiency causes metachromatic leukodystrophy, a rare autosomal recessive disorder characterized by storage of cerebroside sulfate, mainly in the nervous system. Low ASA activities have also been reported in healthy individuals and several neuropsychiatric disorders due to the condition termed ASA pseudodeficiency. The aim of this study was to establish frequency of two mutations associated with ASA pseudodeficiency in healthy individuals in the Croatian population as well as in persons with Alzheimer-type dementia and Down syndrome. Presence of N350S and 1524+95 A G pseudodeficiency mutations was detected in genomic DNA extracted from leukocytes of healthy subjects (n=125) and of patients with Alzheimer-type dementia (n=18) and Down syndrome (n=21). Arylsulfatase A activity was measured in leukocyte homogenates by spectrophotometry (lambda=515 nm) using p-nitrocatechol sulfate as chromogenic substrate. Frequency of N350S mutation and mutation 1524+95 A G was estimated at 6.8 and 2.8% for healthy controls, 11 and 5.5% for Alzheimer-type dementia, and 12 and 9.5% for Down syndrome, respectively. Arylsulfatase A activity was slightly but not significantly decreased in leukocytes derived from subjects with dementia and Down syndrome in comparison with age-matched control samples. Frequency of two mutations associated with ASA pseudodeficiency in the Croatian population is slightly below the range reported for other populations. Additionally, these preliminary results did not show significantly higher frequencies of either mutation in Alzheimer-type dementia or Down syndrome.

Groc L, *Petanjek Z, Gustafsson B, Ben-Ari Y, Hanse E, Khazipov R. In vivo blockade of neural activity alters dendritic development of neonatal CA1 pyramidal cells. Eur J Neurosci 2002;16:1931-8.

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During development, neural activity has been proposed to promote neuronal growth. During the first postnatal week, the hippocampus is characterized by an oscillating neural network activity and a rapid neuronal growth. In the present study the authors tested in vivo, by injecting tetanus toxin into the hippocampus of P1 rats, whether this neural activity indeed promotes growth of pyramidal cells. The authors have previously shown that tetanus toxin injection leads to a strong reduction in the frequency of spontaneous GABA and glutamatergic synaptic currents, and to a complete blockade of the early neural network activity during the first postnatal week. Morphology of neurobiotin-filled CA1 pyramidal cells was analyzed at the end of the first postnatal week (P6-10). In activity-reduced neurons, the total length of basal dendritic tree was three times less than control. The number, but not the length, of basal dendritic branches was affected. The growth impairment was restricted to the basal dendrites. The apical dendrite, the axons, or the soma grew normally during activity deprivation. Thus, the in vivo neural activity in the neonate hippocampus seems to promote neuronal growth by initiating novel branches.

Pivac N, Mück-Šeler D, Sagud M, Jakovljević M. Platelet serotonergic markers in posttraumatic stress disorder. Prog Neuropsychopharmacol Biol Psychiatry 2002;26:1193-8.

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The neurobiological basis of posttraumatic stress disorder (PTSD) is believed to involve alterations in different neurotransmitter systems, and recent studies elucidated the role of serotonin (5-hydroxytryptamine, 5-HT) in PTSD. The reports suggested that platelet 5-HT concentration and monoamine oxidase (MAO) activity might serve as biological, even trait, markers for particular mental disturbances. Since the data on the peripheral serotonergic markers in PTSD subjects are controversial, the aim of the study was to determine platelet 5-HT concentration and platelet MAO activity in war veterans with PTSD, war veterans who did not develop PTSD, and in war veterans who were prisoners of war and developed PTSD. Platelet 5-HT concentration and MAO activity did not differ significantly between war veterans with or without PTSD, and prisoners of war with PTSD. Clinician-Administered PTSD Scale (CAPS) scores did not differ between war veterans with PTSD and prisoners of war, but Montgomery-Asberg Depression Rating Scale (MADRS) scores were significantly higher in prisoners of war who developed PTSD than in war veterans with PTSD. There was no significant correlation between platelet 5-HT concentration or platelet MAO activity and CAPS or MADRS scores within these groups. Platelet 5-HT concentration was slightly higher and platelet MAO activity slightly lower in prisoners of war with PTSD, than in all other groups. These findings suggest that platelet 5-HT concentration and platelet MAO activity are not altered in three drug-free groups—war veterans who did or did not develop PTSD, or in prisoners of war with PTSD—and that these platelet serotonergic markers are not associated with symptoms of PTSD or comorbid depression.

Vladić A, Horvat G, Vukadin S, Sučić Z, Šimaga S. Cerebrospinal fluid and serum protein levels of tumour necrosis factor-alpha(TNF-alpha), interleukin-6 (IL-6) and soluble interleukin-6 receptor (sIL-6R gp80) in multiple sclerosis patients. Cytokine 2002;20:86-9.

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The aim of this study was to evaluate soluble proteins - tumour necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6) and IL-6 receptor subunit gp80 (sIL-6R gp80) – as markers of multiple sclerosis (MS). Paired cerebrospinal fluid (CSF) and serum samples of 20 MS patients and 15 controls suffering from non-inflammatory neurological diseases have been assayed retrospectively using monoclonal antibodies-based ELISAs. While TNF-alpha could not be detected in CSF, it was measurable in 20% of total sera. Interleukin-6 was measurable in 5% of total CSF and in 10% of total sera only. However, soluble IL-6R gp80 protein subunit was readily measurable, showing sera concentration (pg/mL) about 34 times higher and specific content (pg/mg total protein) around five times lower than those in paired CSF, similarly for both group of patients. No significant difference of sIL-6R gp80 level, which could be disease-, gender- or age-related, and no correlation of CSF sIL-6R gp80 content with that of paired serum or with routine clinical data for CSF, have been observed. The authors conclude that soluble proteins of TNF-alpha, IL-6 and sIL-6R gp80 assayed by monoclonal antibodies-based ELISAs could not serve as markers of the MS activity.

Hasan M, Polić B, Bralić M, *Jonjić S, Rajewsky K. Incomplete block of B cell development and immunoglobulin production in mice carrying the muMT mutation on the BALB/c background. Eur J Immunol 2002;32:3463-71.

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The expression of the pre-B cell receptor (pre-BCR), composed of the mu chain, surrogate light chains and the Ig-alpha /Ig-beta signal transduction unit, permits further differentiation of B-cell precursors. C57BL/6 mice homozygous for an inactivating mutation of the membrane exon of the mu chain gene (C57BL/6muMT/muMT)) cannot form a pre-BCR and are, consequently, devoid of mature B-lymphocytes. Here the authors present evidence that the block of B-cell development by the muMT mutation is incomplete in BALB/c mice. Unlike C57BL/6muMT/muMT, BALB/cmuMT/muMT mice generate small numbers of mature B-cells, accumulate plasma cells and produce high levels of all immunoglobulin isotypes, except IgM. The observed phenomenon seems to be controlled by a single genetic locus that is not linked to IgH.

***Milošević D, Rinat C, Batinić D, Frishberg Y. Genetic analysis – a diagnostic tool for primary hyperoxaluria type I. Pediatr Nephrol 2002;17:896-8.**

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Primary hyperoxaluria type I is an autosomal recessive metabolic disease in which excessive oxalates are formed by the liver and excreted by the kidneys, causing a wide spectrum of disease, ranging from renal failure in infancy to mere renal stones in late adulthood. The diagnosis may be suspected when clinical signs and increased urinary oxalate and glycolate excretion present, and is confirmed by the measurement of decreased alanine:glyoxylate aminotransferase activity in a liver sample. The enzymatic assay is not readily available to pediatric nephrologists in many parts of the world. The authors describe three families from Croatia in whom the diagnosis of primary hyperoxaluria was solely based on clinical findings that included nephrolithiasis and nephrocalcinosis accompanied by increased urinary oxalates and glycolate excretion, as enzymatic assays of liver samples could not be performed. Mutation analysis of the AGXT gene encoding the defective enzyme confirmed the diagnosis, revealing three alleles carrying the C156ins mutation and two the G630A mutation. Screening first-degree relatives for the relevant mutation disclosed an asymptomatic affected sibling. Mutation analysis of the AGXT gene is a non-invasive and accurate tool for the diagnosis of type I primary hyperoxaluria that may replace enzymatic assays of liver biopsies.

***Sabolić I, Ljubojević M, Herak-Kramberger CM, Brown D. Cd-MT causes endocytosis of brush-border transporters in rat renal proximal tubules. Am J Physiol Renal Physiol 2002;283:F1389-402.**

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The authors have recently proposed that Cd may impair the vesicle-dependent recycling of BBM transporters by inhibiting vacuolar H + ATPase (V-ATPase) activity and endocytosis in PT cells (Herak-Kramberger CM, Sabolic I, and Brown D. Kidney Int 53:1713-1726, 1998). The mechanism underlying the Cd effect was further explored in an in vivo model of experimental Cd nephrotoxicity induced by Cd-metallothionein (Cd-MT; 0.4 mg Cd/kg body mass; a single dose sc) in rats. The time-dependent redistribution of various BBM transporters was examined in this model by fluorescence and gold-labeling immunocytochemistry on tissue sections and by immunoblotting of isolated renal cortical BBM. In PT cells of Cd-MT-treated rats, the authors observed 1) shortening and loss of microvilli; 2) time-dependent loss of megalin, V-ATPase, aquaporin-1 (AQP1), and type 3 Na exchanger (NHE3) from the BBM; 3) redistribution of these transporters into vesicles that were randomly scattered throughout the cell cytoplasm; and 4) redistribution of NHE3, but not megalin, into the basolateral plasma membrane. The internalization of BBM transporters was accompanied by fragmentation and loss of microtubules and by an increased abundance of alpha-tubulin monomers in PT cells. Transporter redistribution was detectable as early as 1 h after Cd-MT treatment and increased in magnitude over the next 12 h. The authors conclude that the early mechanism of Cd toxicity in PT cells may include a colchicine-like depolymerization of microtubules and impaired vesicle-dependent recycling of various BBM proteins. These processes may lead to a time-dependent loss of cell membrane components, resulting in reabsorptive and secretory defects that occur in Cd-induced nephrotoxicity.

Kozarić-Kovačić D, Karlović D, Kocijan-Hercigonja D. Elevation of serum total triiodothironine and free triiodothironine in Croatian veterans with combat-related post-traumatic stress disorder. Mil Med 2002;167:846-9.

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The objective of this study was to asses possible differences in serum-free triiodothironine (FT3), total triiodothironine (TT3), free thyroxine, total thyroxine, and thyroid-stimulating hormone levels between male combat veterans with chronic post-traumatic stress disorder and healthy male control subjects. Male combat veterans (n = 38; age: range 23-53 years, mean SD = 35.9 7.5 years) with chronic post-traumatic stress disorder (duration of illness was 2-6 years; mean SD = 3.53 0.95 years) were compared with healthy male control subjects (n = 32; age: range 25-50 years; mean SD = 36.5 8.3 years). Serum samples were analyzed by luminoimmunochemical assays for basal levels of thyroid-stimulating hormone, total thyroxine, TT3, free thyroxine, and FT3. Combat veterans with chronic combat-related post-traumatic stress disorder had significantly increased values of FT3 (mean SD = 5.92 1.11; $t = 2.27$; $p < 0.02$), as well as TT3 (mean SD = 2.04 0.32; $t = 6.26$; $p < 0.0001$) than the control group. In conclusion, elevated serum TT3 and FT3 are associated with chronic combat-related post-traumatic stress disorder.

Raos V, Strujić BJ. Dyslipoproteinemia and coronary disease. Angiology 2002;53:557-62.

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The aims of this study were to evaluate the relations among the plasma lipids, their fraction Apo A1, HDL, and positive coronary arteriography, and to estimate their importance as markers of the degree of coronary lesions. The study included 101 subjects, 77 men and 24 women, aged 35 to 75 years, mean age of 55.7 years. The subjects were divided into 2 groups: 1 group - CAD with positive coronary arteriography (n = 70), and the other group - CAD with negative coronary arteriography (n = 31). According to the anatomic localization of atherosclerotic lesion, the first group of subjects was divided into 1-vessel (n = 26), 2-vessel (n = 20), and multiple-vessel lesion (n = 24) subgroups. The results show a significant difference in Apo A1 and Apo A1/Apo B ($p < 0.005$) in the 2- and multiple-vessel disease in relation to the control group, while subject significance was not proved for 1-vessel disease. A positive correlation and significance for HDL as well as cholesterol ratio/HDL ($p < 0.05$) was noted for 1- and multiple-vessel disease, while a negative correlation was noted for 2-vessel disease in relation to the control group. This study stressed the diagnostic significance in determining Apo A1 and Apo A1/Apo B1 as better predictors than HDL cholesterol in evaluating coronary lesion severity. Dyslipoproteinemia, namely, the level of lipoproteins of low density, plays an important role in the pathogenesis of arteriosclerosis and the development of CAD.

Hečimović S, Klepac N, Vlašić J, Vojta A, Janko D, Škarpa-Prpić I, et al. Genetic background of Huntington disease in Croatia: molecular analysis of CAG, CCG, and Delta2642 (E2642del) polymorphisms. Hum Mutat 2002;20:233.

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This study presents the first molecular data on the basis and the origin of Huntington disease in Croatia and is the first such analysis performed among a Slavic population. The authors analyzed three trinucleotide polymorphisms in the HD gene: CAG, CCG and GAG Delta2642 (E2642del) triplets. Analysis of the CAG repeat size among 44 Huntington patients (39-66 CAGs) and 51 normal individuals (9-34 CAGs) showed that the range of the repeats was similar to previous findings. The frequency of the CCG and Delta2642 polymorphic alleles on N and HD chromosomes was found to correlate well with earlier reports for Western European populations. The authors found significance for both the CCG7 allele ($p = 0.004$) and the Delta2642 allele ($p < 0.001$) among HD chromosomes. The CCG7 allele was overpresented among affected chromosomes (94.6%), but was also the most frequent CCG allele among normal chromosomes (66.7%). Interestingly, the Delta2642 allele was present on 40.5% HD chromosomes compared to only 9.8% of control chromosomes. These results indicate that HD mutations in Croatia could be of the same origin as in Western populations and also support the multi-step hypothesis for generating new HD alleles. Similar frequencies and distributions of both the CCG and the Delta2642 polymorphisms in Croatia and Western European normal chromosomes indicate that the prevalence rate of HD in Croatia may be as high as in Western populations.

Klapan I, Šimičić L, Rišavi R, Bešenski N, Pasarić K, Gortan D, et al. Tele-3-dimensional computer-assisted functional endoscopic sinus surgery: new dimension in the surgery of the nose and paranasal sinuses. Otolaryngol Head Neck Surg 2002;127:549-57.

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One of the main objectives of the authors 3-dimensional (3D) computer-assisted functional endoscopic sinus surgery was to design a computer-assisted 3D approach to the presurgical planning, intraoperative guidance, and postoperative analysis of the anatomic regions of the nose and paranasal sinuses. Such an extremely powerful approach should allow better insight into the operating field, thereby significantly increasing the safety of the procedure. The last step to implementing the technology in the operating room was to connect the computer workstations and video equipment to remote locations by using a high-speed, wide-bandwidth computer network. During patient preparation, the surgeon in the operating room consulted remote experienced and skillful surgeons by viewing CT images and 3D models on computer workstations. The surgeon and consultants used software for CT image previews and 3D model manipulations on top of collaboration tools to define the pathosis, produce an optimal path to the pathosis, and decide how to perform the real surgical procedure. With tele-flythrough or tele-virtual endoscopy rendered through the use of 3D models, both surgeons can preview all the characteristics of the region and so predict and determine the next steps of the operation. This ensures greater safety thanks to the operation guidance and reduces the possibility of intraoperative error. The duration of the teleconsultation is thus shortened, which may prove the greatest benefit of tele-3D computer-assisted surgery. If this method were used, clinical institutions would spend less money for telesurgical consultation.

***Tokmadžić VS, Tsuji Y, Bogović T, Laškarin G, Ćupurdija K, Štrbo N, et al. IL-18 is present at the maternal-fetal interface and enhances cytotoxic activity of decidual lymphocytes. Am J Reprod Immunol 2002;48:191-200.**

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The aim of the study was to investigate the presence and role of interleukin 18 (IL-18) on NK cytolytic potential at maternal-fetal (M-F) interface. Peripheral blood cells and decidual tissue were obtained from elective pregnancy termination of normal human 6-10-week-old pregnancies. Perforin expression and cytolytic activity of peripheral blood (PBL) and decidual lymphocytes (DL) were analyzed by flow cytometry. IL-18 positive decidual adherent cells (DAC) were detected by the same method. IL-18 and IL-18 receptor (IL-18R) expression on the trophoblastic cells was detected by immunohistology using biotinylated anti-IL-18 and IL-18R monoclonal antibodies. The IL-18 added in a dose of 10 ng/mL up-regulates perforin expression and cytolytic activity of DL. Simultaneous stimulation with IL-18 and IL-12 enhanced DL cytolytic activity, while IL-18 combined with IL-10 or IL-15 did not show this effect. Cytolytic activity of PBL was up-regulated by IL-18 as well, and this effect was enhanced by the addition of IL-12 and IL-15. Interleukin-18 did not affect perforin-protein expression in cultured PBL. Approximately 20% of DAC were IL-18 positive and these cells were mostly human leukocyte antigen (HLA)-DR negative. IL-18R positive cells were found on syncytiotrophoblast cell layer, interstitial tissue cells of villi and fetal blood cells. There was no detectable IL-18 staining on trophoblast cell layer on villi, but strong staining of fetal blood cells in villous vessels. In conclusion, these are first results showing IL-18R expression, but not IL-18 expression on villous trophoblastic cells, as well as enhancement of perforin expression and NK cytolytic potential of DL under the influence of IL-18. IL-18 in concert with other cytokines and hormones could play an important role in the regulation of cytolytic potential of first trimester pregnancy decidual and peripheral blood NK cells.