Filić V, Vladić A, Štefulj J, Čičin-Šain L, Balija M, Sučić Z, et al. Monoamine oxidases A and B gene polymorphisms in migraine patients. J Neurol Sci. 2005;228:149-53.

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Abnormal cortical activity and brainstem functioning are considered the possible etiopathogenetic factors of migraine. Monoamine oxidase A and B (MAO-A and -B) regulate the levels of monoamine neurotransmitters, so changes in their activity could participate in migraine pathogenesis. We have investigated the possible association of MAO-A and -B alleles and haplotypes with two common types of migraine, ie migraine without aura (MO) and migraine with aura (MA), on the sample of 110 migraineours (80 MO and 30 MA) and 150 controls. MAO-A promoter and MAO-B intron 13 polymorphisms were genotyped by the PCR-based methods. In addition, we have reevaluated the reported association between MAO-B intron 13 polymorphism and platelet MAO-B activity. The platelet MAO-B activity was determined fluorimetrically using kynuramine as a substrate. The authors found a tendency toward association of the shorter variant of MAO-A gene promoter with migraine without aura in male subjects. Regarding investigated MAO-B polymorphism, no association with migraine or with platelet MAO-B activity was found. The suggestive association of the variant in MAO-A gene with migraine is considered worthy of independent replication. On the other hand, further studies on MAO-B polymorphism in migraine do not seem promising.

Krušlin B, Tomas D, Rogatsch H, Reljić A, Vučić M, Baličević D, et al. Correlation of periacinar retraction clefting in needle core biopsies and corresponding prostatectomy specimens of patients with prostatic adenocarcinoma. Int J Surg Pathol. 2005;13:67-72.

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One of the underemphasized supportive criteria for the diagnosis of prostatic cancer is the presence of retraction clefting around neoplastic glands. We analyzed a series of 152 prostatic cancer cases to determine the frequency, extent, and correlation of periacinar retraction clefting between needle core biopsies (NCB) and corresponding matched radical prostatectomy (RP) specimens. Clefting was significantly more frequent in neoplastic compared to nonneoplastic acini in NBC and RP ($p < 0.05$). There was no significant difference in the frequency of retraction clefting in neoplastic acini between NCB and corresponding RP ($p > 0.05$). We have also found a concordance in matched RP and NCB (kappa = 0.582). We conclude that periacinar retraction clefting appears more frequently in neoplastic acini and could serve as a reliable criterion in the diagnosis of prostatic adenocarcinoma.

Vrdoljak E, Prskalo T, Omrčen T, Šitum K, Boraska T, Frleta Ilić N, et al. Concomitant chemobrachyradiotherapy with ifosfamide and cisplatin followed by consolidation chemotherapy in locally advanced squamous cell carcinoma of the uterine cervix: results of a phase II study. Int J Radiat Oncol Biol Phys. 2005;61:824-9.

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The aim of this study was to evaluate the efficacy and toxicity of ifosfamide and cisplatin administered concomitantly with low-dose-rate brachytherapy followed by consolidation chemotherapy in the treatment of locally advanced squamous cell cervical carcinoma (LASCC). Forty-four patients with biopsy-proven LASCC were enrolled. FIGO stages IB2 bulky to IVA were entered into this study. Patients were assigned to receive external radiotherapy (50 Gy in 25 fractions); then ifosfamide 2 g/m^2 plus cisplatin 75 mg/m^2 was applied during two low-dose-rate brachytherapy applications, and 4 cycles of consolidation chemotherapy with the same drug combination were given after completion of radiotherapy. The planned dose to point A was 85 Gy. All patients received both courses of concomitant chemobrachytherapy and at least 1 cycle of consolidation chemotherapy. The average duration of radiation was 45.1 days. The clinical complete response rate was 100%. Grade 3 and 4 leukopenia occurred in 25% and

11% of the cycles, respectively. After a median follow-up of 34 months (range, 20-54 months), the recurrence-free and the overall survival rates were 84% and 91%, respectively. Major delayed local complications occurred in 7 cases (16%). These results indicate that concomitant chemobrachyradiotherapy with ifosfamide and cisplatin is a feasible combination for patients with LASCC of the cervix uteri. A randomized trial is planned.

Barišić N, Muller JS, Paučić-Kirinčić E, Gazdik M, Lah-Tomulić K, Pertl A, et al. Clinical variability of CMS-EA (congenital myasthenic syndrome with episodic apnea) due to identical CHAT mutations in two infants. Eur J Paediatr Neurol. 2005;9:7-12.

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Congenital myasthenic syndromes (CMS) result from mutations in various synapse-associated genes. Mutations in the choline acetyltransferase (CHAT) gene cause a presynaptic CMS associated with episodic apnea (CMS-EA). The authors present two unrelated Croatian children affected by CMS-EA. Beside other clinical findings characteristic for CMS, both patients manifested intermittent apneas since early infancy. Whereas the course of disease is mild in the female patient (pt.#2), the male patient (pt.#1) experienced recurrent and severe episodes of apnea despite adequate treatment with AChE-inhibitors and shows a global developmental delay with delayed myelination and signs of hypoxic-ischemic injury in brain imaging. Interestingly, sequencing of the CHAT gene revealed identical, compound heterozygous mutations S694C and T354M in both children. These findings are in line with a remarkable clinical heterogeneity observed in patients with CHAT mutations and emphasize the potential role of apneic crises for the development of secondary hypoxic brain damage and psychomotor retardation.

Radić V, Čanić T, Valetić J, Duić Z. Advantages and disadvantages of hysterosono-salpingography in the assessment of the reproductive status of uterine cavity and Fallopian tubes. Eur J Radiol. 2005;53:268-73.

Merkur University Hospital, Zagreb, Croatia

In a prospective study, 68 patients in the initial stage of the infertility treatment were examined by hysterosonosalpingography using saline NaCl infundibile and Echovist as contrast media. Subsequently, further status of the tubes and uterine cavity was assessed by the "gold standards", laparoscopy and hysteroscopy. Sensitivity and specificity of hysterosonosalpingography using NaCl infundibile for evaluation of the uterine cavity was 100 and 88.8%, respectively. Negative predictive value was 100% and positive predictive value 97%. Sensitivity and specificity of the method for the assessment of the tubal status was 100 and 66%, respectively, negative predictive value was 100% and positive predictive value was 61%. For the assessment of tubal patency using positive contrast Echovist the method has shown 100% sensibility and negative predictive value again but it reached a specificity of 77% and a positive predictive value of 70%. There were no evident complications during or after the procedure. In conclusion, hysterosonosalpingography is useful in making decisions regarding further procedures for the diagnosis and treatment of infertility. Uterine cavity evaluation using saline is the method of choice. Tubal patency can be assessed only under ideal sonographic conditions. The method is feasible for early assessment of the reproductive status of uterine cavity and fallopian tubes as a simple, safe and cheap outpatient method prior to any following invasive procedure or even histerosalpingography.

Šimić G, Bexheti S, Kelović Z, Kos M, Grbić K, Hof PR, et al. Hemispheric asymmetry, modular variability and age-related changes in the human entorhinal cortex. Neuroscience. 2005;130:911-25.

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The authors analyzed the verrucae areae entorhinalis (VAE) in 60 neurologically normal subjects ranging from 23 to 85 years of age using a casting method. In 10 of these subjects the total number of neurons in the entorhinal islands was estimated stereologically using the optical fractionator. The number and surface area of VAE were higher in the left hemisphere compared with the right, and this leftward asymmetry was highly significant. Regression analysis showed a negative correlation between average VAE area and age in both hemispheres, representing a rate loss of about 800 microm^2 per year. The estimated number of neurons obtained with the optical fractionator showed no significant difference between the left and the right hemisphere (468,000144,000 vs. 405,000117,000). There was a highly significant negative correlation between neuron numbers and age in both sides. In addition, clusters of small, undifferentiated layer II neurons ('heterotopias') were frequently observed in the rostral part of the entorhinal cortex in young and elderly adults. Layer II entorhinal neurons are among the first to show neurofibrillary changes during normal aging. The present data confirm the occurrence of age-related neuron loss in the entorhinal cortex. Considering the consistent projections from ipsilateral auditory association areas that, together with Broca's motor-speech area (Brodmann areas 44 and 45), show leftward asymmetry from early infancy (such as Brodmann area 22, planum temporale, and area 52 in the long insular gyrus), the authors speculate that functional lateralization of the human entorhinal cortex may be associated with specialization for memory processing related to language. Due to the dependence of hippocampal formation on entorhinal projections, this finding is also consistent with the greater capacity of the left hippocampus for verbal episodic memory.

Forčić D, Ivančić J, Baričević M, Mahovlić V, Tešović G, Božinović D, et al. Genetic characterization of wild type measles virus isolated in Croatia during the 2003-2004 outbreak. J Med Virol. 2005;75:307-12.

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Viral epidemiology is determined by the movement of infected people within and between geographical areas. The genetic characterization of wild-type isolates combined with standard epidemiological methods may enable the identification of the source and transmission pathways and permit differentiation between indigenous and imported viruses. The authors investigated the genetic characteristics of the wild-type measles virus isolated in Croatia during a 2003-2004 outbreak. The results of this study indicate the presence of the D4 measles virus genotype in Europe. The isolated virus is closely related to virus isolates from the India-like subgroup of the D4 measles virus genotype. The virus responsible for this outbreak differs in the hemagglutinin gene sequence from other virus strains belonging to the D4 genotype. The hemagglutinin gene sequence also differs when compared to viruses from other genotypes that are known to circulate in Europe and from vaccine strains.

Magdalenić-Meštrović M, Bagatin M. An epidemiological study of orofacial clefts in Croatia 1988-1998. J Craniomaxillofac Surg. 2005;33:85-90.

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The aim of the present study was to analyse the character and incidence of orofacial clefts in Croatia and to compare the data with reports from other countries. All the material for the epidemiological study was retrieved from the documented files from all the neonatal units and hospitals in Croatia providing surgical treatment. A total of 525,298 livebirths were documented during 11 years (1988-1998); 903 among them with orofacial clefts, 24 (2.7%) of them twins. Sixty (6.6%) infants died between birth and the age of 6 months. The incidence of orofacial clefts during the study period was 1.71 per thousand. When eliminating syndromic clefts, the incidence of non-syndromic clefts was 1.56 per thousand. Analysis of cleft lip with or without cleft palate (CL+/-P) and isolated cleft palate only (CP) revealed their incidence to be 1.05 and 0.66 per 1000, respectively. Of all types of clefting, CL and CLA was found in 17.2%, CL+/-P in 43.9%, CP in 38.2% and atypical facial clefts (AFC) in 0.8% of children. Left-sided clefts were most common (51%), followed by bilateral (30.5%) and right-sided (18.5%) clefts. The male to female ratio was 1.3. CL+/-P predominated in male and CP in female children. In 220 cases (24.4%) orofacial clefts were either associated with other anomalies or the clefts occurred as one feature of a syndrome. The data obtained from different sources yielded a cleft incidence of 1.71 per 1000 in Croatia. There were no differences in the incidences of orofacial clefts in comparison with similar data from other European countries.

Brnić Z, Gašparov S, Lozo PV, Anić P, Patrlj L, Ramljak V. Is quadrant biopsy sufficient in men likely to have advanced prostate cancer? Comparison with extended biopsy. Pathol Oncol Res. 2005;11:40-4.

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The aim of this study was to investigate whether the reduction of core number in first-line PB from 6-12 to 4 in patients with presumed advanced PC leads to loss of clinically relevant information. The authors retrospectively studied 113 men that underwent PB, classified in two groups: "H" (high) and "L" (low likelihood of having advanced PC), according to PSA, digital rectal and transrectal ultrasound findings. Pathological results of 6-12-core PB and QPB were retrospectively compared for the presence of malignancy, percentage of positive cores, Gleason score (GS), and the presence of high-grade prostatic intraepithelial neoplasia (HGPIN). PC detection rate was not impaired in group H but dropped significantly in group L, and the percentage of positive cores was not significantly changed in group H ($p=0.39$), but decreased in group L ($p=0.04$), due to sampling scheme reduction. No HGPIN was missed with QPB in group H, while 2 HGPINs were missed in group L. No significant change in GS in either group was observed ($p=0.12$, $p=0.13$) due to reduction to QPB. The autrhors conclude that in patients with presumed advanced PC, reduction of the number of cores in PB may be an acceptable diagnostic strategy, but further studies are needed to analyze the impact of PB scheme reduction on other relevant pathological information obtained from PB.

Štefulj J, Kubat M, Balija M, Škavic J, Jernej B. Variability of the tryptophan hydroxylase gene: study in victims of violent suicide. Psychiatry Res. 2005;134:67-73.

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Tryptophan hydroxylase (TPH), the enzyme controlling serotonin synthesis, is considered to be a potential contributor to the biological substrate of suicide. The association of the promoter (-7065ct) and intron 7 (218ac) polymorphisms, and the related haplotype, of the Tph1 gene with suicidal behavior was investigated in a sample of 160 victims of violent suicide and 284 healthy controls. All individuals were males of Croatian (Slavic) origin. Allele frequencies of both polymorphisms in Croatian controls were similar to control values reported for other European populations. Alleles at the two loci demonstrated highly significant linkage disequilibrium. No differences between controls and victims for the Tph1 genetic variation, either at single loci, or at a haplotypic level, were demonstrated, albeit there was a tendency, not reaching statistical significance, towards an increase of the intron 7cc genotype in the suicide group. Negative association results on the individ-

ual Tph1 loci, in accordance with the majority of previous reports, confirmed the lack of their major effect also in the Slavic ethnicity. Haplotypic results, on the other hand, opposing the previous positive finding, point to the possible influence of ethnicity (or gender) on the association between the Tph1 gene polymorphism and suicide.

Pećina-Šlaus N, Nikuševa-Martić T, Gall-Trošelj K, Radić K, Hrašćan R. Replication error-positive samples found in pheochromocytomas. In Vivo. 2005;19:359-65.

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Adenomatous polyposis coli, (APC) and E-cadherin (CDH1) tumor suppressor genes were investigated in human pheochromocytoma. Both genes are components of adherens junctions, but are also involved in wnt signalling in which one of the target molecules is c-myc protein. Fifteen sporadic pheochromocytomas were tested for gene instability by PCR/loss of heterozygosity. Detection of c-myc protein was performed using immunohistochemistry. One sample with allelic imbalance of the APC gene and one with allelic imbalance of the CDH1 gene were found. Interestingly, another type of genomic instability was detected – replication error-positive samples (RER+). Four out of 13 heterozygous samples were RER-positive (30.8%). The instability is the result of impaired cellular mismatch repair. Immunohistochemistry showed increased levels of c-myc in comparison to normal adrenal tissue. These results suggest that microsatellite genetic instabilities of the E-cadherin gene have a role in pheochromocytoma development and progression. Detected instability indicates that mismatch repair may be targeted in pheochromocytoma. Increased expression of c-myc protein as well as allelic imbalances of APC and CDH 1 genes suggest that the wnt signalling pathway may have a role in this malignancy.

Gabrilovac J, Breljak D, Čupić B, Ambriović-Ristov A. Regulation of aminopeptidase N (EC 3.4.11.2; APN; CD13) by interferon-gamma on the HL-60 cell line. Life Sci. 2005;76:2681-97.

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This study addressed the effects of a T-cell derived cytokine, interferon-gamma (IFN-gamma) on the activity of aminopeptidase N (APN), an ectoenzyme processing several signal peptides. Cells of a myelo-monocytic cell line HL-60 were used as a model system, and APN was assayed at the levels of mRNA, its membrane marker CD13, and the enzyme activity. Regulation of CD13/APN by IFN-gamma was found at all three levels. The direction of regulation was time-dependent: an initial down-regulation seen 24 and 48 hrs after the onset of treatment with IFN-gamma was replaced by an up-regulation after 72 and/or 96 hrs. Up-regulation of CD13/APN observed after 96 hrs was preceded by an up-regulation of APN mRNA reaching its maximum after 72 hrs. The IFN-gamma-induced regulation of APN was due to membrane aminopeptidase N, since it could be completely abrogated by an APN blocking antibody WM-15. The delayed up-regulation of CD13/APN (observed after 72 and/or 96 hrs), required de novo protein synthesis as it could be abrogated by cycloheximide, an inhibitor of protein synthesis. Possible role of endogenous (IFN-gamma-induced) TGF-beta in mediating CD13/APN up-regulation could be excluded, since no TGF-beta was found in supernatants of IFN-gamma treated HL-60 cells. Thus, these data show regulation of CD13/APN on cells of myelo-monocytic origin by a T-cell derived cytokine, IFN-gamma. A similar mechanism might play a role in inflammation.

Laškarin G, Čupurdija K, Tokmadžić VS, Dorčić D, Dupor J, Juretić K, et al. The presence of functional mannose receptor on macrophages at the maternal-fetal interface. Hum Reprod. 2005;20:1057-1066.

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The mannose receptor (MR) is involved in the initiation of the immune response and regulation of homeostasis during inflammation and tissue remodeling. Distribution, endocytosis and possible natural ligand tumor associated glycoprotein-72 (TAG-72) for the MR have been examined by immunohistology, immunocytochemistry and flow cytometry at the maternal-fetal interface, characterized by extensive tissue remodeling. Contrary to disseminated distribution of the MR positive (MR+) cells in term placenta, the MR+ cells of early pregnancy decidua intimately surrounded glands and followed tissue distribution of CD14 positive cells. The mannose receptor was present on freshly isolated first trimester decidual mononuclear cells and distributed mostly on macrophages (77.08 +/- 10.55%, mean +/- SD). The expression of the MR on CD14 positive cells decreased following 18 h culture ($p < 0.01$) and was accompanied by the reduction of fluorescein isothiocyanate (FITC)-dextran uptake. PAM-1 anti-MR antibody, mannan and TAG-72 reduced FITC-dextran uptake by decidual macrophages. These data indicate that the MR+ macrophages, surrounding early decidual glands, are able to internalize ligands for carbohydrate recognition domain of the receptor, including decidual secretory phase mucin TAG-72.