

**Hranilović D, Štefulj J, Furač I, Kubat M, Bališa M, Jernej B. Serotonin transporter gene promoter (5-HTTLPR) and intron 2 (VNTR) polymorphisms in Croatian suicide victims. *Biol Psychiatry* 2003;54:884-9.**

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The disturbances in serotonin (5HT) transmission are the most frequently reported neurobiological substrates of suicidal behavior. Because 5HT transporter plays a central role in the regulation of 5HT synaptic function and its gene contains two functional polymorphisms (5-HTTLPR in the promoter region and VNTR in the second intron), it represents an interesting candidate for association studies in suicidal behavior. In this study, a possible association of 5-HTTLPR and intron 2-VNTR polymorphisms of the 5HT transporter gene with suicidal behavior was investigated in a sample of 135 suicide victims and 299 healthy control subjects of Croatian/southern Slavic origin. There were no significant differences in 5-HTTLPR and intron 2-VNTR genotype- and allele- frequency distributions between suicide victims and healthy control subjects; however, a tendency toward an increase of 5-HTTLPR allele L and VNTR-allele 10 were observed in suicide group. Analysis of distribution of estimated haplotype frequencies revealed differences between suicide victims and control subjects, with an excess of haplotype L10 among suicide victims ( $p = .0112$ ). In conclusion, these results provide modest evidence for a possible association of the 5HT transporter gene with a completed suicide. Further studies are needed to determine whether alterations in 5HTT gene expression are involved in suicidal behavior.

**Bedenić B, Vranješ J. Post-exposure effects of cefepime and ceftiofime on isogenic *Escherichia coli* hosts producing SHV-extended-spectrum beta-lactamases. *J Chemother* 2003;15:342-9.**

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Persistent suppression of bacterial growth after short antimicrobial exposure is called postantibiotic effect (PAE). By definition, there should be no subinhibitory concentrations of antimicrobial agent left when the postantibiotic effect starts. However, if subinhibitory concentrations are maintained after removing the antibiotic, the recovery period of the treated cultures is markedly prolonged. This is defined as postantibiotic-sub-MIC-effect (PA-SME). The aim of this study was to determine the PAE and PA-SME of ceftiofime and cefepime on isogenic *Escherichia coli* strains producing SHV-2, SHV-5, and SHV-12 extended spectrum beta-lactamases (ESBL) compared to a non-ESBL *E. coli* strain. It was hypothesized that the presence of an ESBL would hydrolyze the cephalosporin molecule before it exerted a toxic effect on the bacterial cell and thus shorten the duration of PA-SME. Ceftiofime and cefepime had no PAE against ESBL producing *E. coli* or it was of a short duration and present only at high antibiotic concentrations, but exposure to subinhibitory concentration of those antibiotics in the PA (postantibiotic) phase resulted in a significant delay of regrowth. The effect was more pronounced with higher concentrations of antibiotics, and uninfluenced by the type of enzyme and the antibiotic. The present study shows that the pres-

ence of subinhibitory concentrations of ceftiofime and ceftiofime in the medium after exposure to supra-inhibitory concentrations results in a significant delay of regrowth of both ESBL-positive and negative *E. coli* strains. The production of SHV-2, SHV-5 and SHV-12 ESBLs did not shorten the duration of the PA-SME.

**Božanić D, Tafra R, Saraga-Babić M. Role of apoptosis and mitosis during human eye development. *Eur J Cell Biol* 2003;82:421-9.**

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The spatial and temporal distribution as well as ultrastructural and biochemical characteristics of apoptotic and mitotic cells during human eye development were investigated in 14 human conceptuses of 4-9 postovulatory weeks, using electron and light microscopy. In the 5th developmental week, apoptotic and mitotic cells were found in the neuroepithelium of the optic cup and stalk, being the most numerous at the borderline between the two layers of the optic cup, and at the place of transition of the optic cup into stalk. They were also found at the region of detachment of the lens pit from the surface ectoderm. In the later developmental stages (the 6th-the 9th week), apoptotic and mitotic cells were observed in the neural retina and the anterior lens epithelium. Throughout all stages examined, mitotic cells were found exclusively adjacent to the lumen either of the intraretinal space or the optic stalk ventricle, or were restricted to the superficial epithelial layer of the lens primordium. Unlike mitotic cells, apoptotic cells occurred throughout the whole width both of the neuroepithelium and the surface epithelium. The distribution of caspase-3-positive cells coincided with the location of apoptotic cells described by morphological techniques indicating that the caspase-3-dependent apoptotic pathway operates during the all stages of human eye development. The location of cells positive for anti-apoptotic bcl-2 protein was in accordance with the regions of eye with high mitotic activity, confirming the role of bcl-2 in protecting cells from apoptosis. In the earliest stage of eye development, apoptosis and mitosis might be associated with the sculpturing of the walls of optic cup and stalk, while high mitotic activity along the intraretinal space and optic stalk ventricle indicates its role in the gradual luminal closure. These processes also participate in the detachment of the lens pit epithelium from the surface ectoderm as well as in further closure of the lens vesicle. Later on, both processes seem to be involved in the neural retina differentiation, lens morphogenesis and secondary lens fibre differentiation.

**Šimaga S, Babić D, Osmak M, Šprem M, Abramić M. Tumor cytosol dipeptidyl peptidase III activity is increased with histological aggressiveness of ovarian primary carcinomas. *Gynecol Oncol* 2003;91:194-200.**

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The aim of this study was to assess activity of DPP III in ovarian tissue specimens and to correlate it with clinico-pathological data. DPP III hydrolytic activity toward Arg-Arg-2-naphthylamide was determined in 108 ovarian tissue cytosol specimens

of 79 patients. The data obtained for 41 ovarian primary carcinoma specimens were stratified according to clinical stage, histological grade and type, and age of the patients. Median DPP III activity expressed as milliunits per milligram protein was 6 in normal ovarian tissues (n=29), 6.5 in benign ovarian tumors (n=19), 19.5 in primary ovarian carcinomas (n=41), 12.5 in nonepithelial primary ovarian tumors (n=7), and 22.1 in metastatic ovarian malignancies (n=12). A significant rise in median DPP III specific activity was observed in malignant ovarian tumors (of epithelial, nonepithelial, and metastatic origin), but not in benign ovarian tumors, compared to the activity in normal tissue. A significant difference of DPP III expression was found between the group of normal tissues and tumors of clinical stage I and II, of grade 2 and 3, of serous and mucinous histologic type. In conclusion, DPP III activity of benign ovarian tumors equaled that in normal ovarian tissue. In malignant neoplasms of the ovary it increased with growing histologic grade.

**Domijan D. A mathematical model of persistent neural activity in human prefrontal cortex for visual feature binding. *Neurosci Lett* 2003;350:89-92.**

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A two-stage model of sustained neural activity in the prefrontal cortex is proposed in order to simulate feature binding and capacity limits in visual working memory. In the first stage, object features are stored in parallel network layers without explicit conjunctions. A second stage binds features into integrated objects consistent with the recent proposal of Wheeler and Treisman (*J Exp Psychol Gen* 2002;131:48). Model neurons have extended dendrites which are capable of active non-linear integration. Computer simulation illustrates model ability to segregate feature values of the different objects into cells with different activity amplitude and to maintain segregated feature representations for a limited number of objects. Depending on the task demands, features are retrieved in a second stage and form a unified object representation.

**Mrakovčić-Šutić I, Šimin M, Radić D, Rukavina D, Radošević-Stašić B. Syngeneic pregnancy induces overexpression of natural killer T cells in maternal liver. *Scand J Immunol* 2003;58:358-66.**

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Conditions such as stress, infection, autoimmune disease, etc. elevate the number and function of extrathymic T cells that are generated mainly in the liver. As primitive, self-reactive clones of T cells that coexpress receptors of the natural killer (NK) lineage, they mediate cytotoxicity against altered self, malignant and infected cells and have the unique potential to rapidly secrete large amount of Th1 or Th2 cytokines. To elucidate whether some of these changes occur even during the syngeneic pregnancy, the authors made phenotypic and functional characterization of mononuclear lymphatic cells (MNLCS) isolated from the liver and spleen of pregnant C57BL/6 mice, testing their cytotoxicity against syngeneic thymocytes as well as against NK- and lymphokine-activated killer (LAK)-sensitive targets. The data have shown that on the sixteenth day of syngeneic pregnancy TCRint, NK1.1+ and IL-2Rbeta+ cells were accumulated in the liver, while the quantities of CD4+ and CD8+ T cells and total number classical NK (NK1.1+CD3- or IL-2Rbeta+CD3-) cells were increased in the spleen. Pregnancy-activated hepatic and splenic MNLCS were more cytotoxic against syngeneic thymocytes, YAC-1 and P815 targets, suggesting that the maternal liver is a main producer of autoreactive NKT clones, which subsequently augment NK- and LAK cell-mediated cytotoxicity in the liver and spleen.

**\*Ambriović-Ristov A, Mercier S, Eloit M. Shortening adenovirus type 5 fiber shaft decreases the efficiency of**

**postbinding steps in CAR-expressing and nonexpressing cells. *Virology* 2003;312:425-33.**

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The coxsackie B virus and adenovirus receptor (CAR) functions as an attachment receptor for multiple adenovirus serotypes. It has been shown that apart from virus-cellular receptor interactions, the fiber shaft length also influences viral tropism. The authors generated Ad5FbDelta639 virus with 8beta-repeats in the shaft, instead of the 22beta-repeats present in the wild-type. Here, they show that the extent of attachment of the virus with shortened fiber to CAR-expressing cells was three- to fivefold lower than that of the wild-type. Transduction studies, however, clearly showed that infection of CAR-expressing cells with Ad5FbDelta639 was strongly impaired by comparison with the wild-type virus. Since this impairment was not linked to a proportional reduction in binding to cells, it appeared to be linked to subsequent/late events in infection. A similar decrease in efficacy of postbinding steps was also evidenced in cells that did not express CAR.

**Macan J, Kanceljak B, Plavec D, Milković-Kraus S. Differences in mite fauna between the continental and Mediterranean climates of Croatia: microscopy and Dustscreen test findings. *Allergy* 2003;58:780-3.**

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The aim of this study was to evaluate the difference between the mite fauna in the inland and coastal Croatia. Ninety-nine floor house dust samples were collected: 28 from the coastal area, 31 from the inland rural and 40 from the inland urban area. Data on basic household characteristics were collected for 81 of 99 households. The mites were separated from the dust using the floatation method and then microscopically identified. The levels of *Dermatophagoides pteronyssinus* (Der p) 1, *Dermatophagoides farinae* (Der f) 1 and Der 2 were measured using the Dustscreen test. Ordinal descriptive statistics and nonparametric tests were used for data analysis, assuming statistical significance at  $p < 0.05$ . More than 70% of mites identified in all areas were pyroglyphids. Nonpyroglyphid mites accounted for 20-25% of all identified mites in the coastal areas (*Blomia*, *Lepidoglyphus* and *Glycyphagus*) and with 15% in the inland areas (*Lepidoglyphus* and *Acarus*). The highest Der p 1 median levels were found in the coastal area, with significantly lower levels in the inland rural and inland urban areas (4.5; 2; 0.85  $\mu\text{g/g}$  of dust;  $p = 0.0001$ ). The highest Der f 1 median levels were found in the inland urban area, with significantly lower levels in the inland rural and coastal areas (0.88; 0.75; 0  $\mu\text{g/g}$  of dust;  $p = 0.0013$ ). The levels of Der f 1 were significantly higher in samples taken from households with central heating than from those with traditional heating (1; 0.25  $\mu\text{g/g}$  of dust;  $p < 0.01$ ). In conclusion, separate diagnostic dust mite lists for the coastal and inland areas because of climatic and dwelling differences required to be implemented. Compared with traditional heating, central heating significantly increases the risk of exposure to Der f 1 levels  $> 2 \mu\text{g/g}$  of dust (odds ratio, 7.35; 95% confidence interval, 1.43-37.87;  $p = 0.01$ ).

**Orlić P, Vukas D, Drescik I, Ivančić A, Blečić G, Budiselić B, et al. Vascular complications after 725 kidney transplantations during 3 decades. *Transplant Proc* 2003;35:1381-4.**

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Among 725 renal transplantations, the most common vascular complication was arterial stenosis, which was observed in 23 patients (3.17%). The majority of 20 (6.49%) arterial stenoses appeared in our initial experiences when we routinely used end-to-end renal graft to internal iliac artery anastomoses. A significant reduction in this incidence (0.72%) was achieved by introducing end-to-side anastomoses of the renal graft artery to the external or common iliac arteries. Intractable hyperten-

sion or impaired renal function in 14 patients (60.87%) with arterial stenosis demanded treatment. Patch angioplasty was more successful than other methods. The limited possibilities of conservative treatment of arterial hypertension at that time were the main reason for this frequent surgical repair. Among other vascular complications, the most serious were 12 episodes of arterial bleeding in 10 patients. Five kidneys were lost because of ruptured arterial anastomoses. In 6 patients, the common or external iliac artery was ligated as to achieve hemostasis with acute arterial insufficiency of the lower extremity in 4 patients. One patient required leg amputation, whereas 2 underwent extra-anatomic bypass procedures and 1 died because of hepatic failure. The majority of vascular complications occurred in the initial period of transplantation practice. However, in spite of progress in diagnostic and treatment options, vascular complications may cause considerable clinical problems.

**\*Barac L, Peričić M, Klarić IM, Rootsi S, Janičijević B, Kivisild T, et al. Y chromosomal heritage of Croatian population and its island isolates. Eur J Hum Genet 2003;11:535-42.**

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Y chromosome variation in 457 Croatian samples was studied using 16 SNPs/indel and eight STR loci. High frequency of haplogroup I in Croatian populations and the phylogeographic pattern in its background STR diversity over Europe make Adriatic coast one likely source of the recolonization of Europe following the Last Glacial Maximum. The higher frequency of I in the southern island populations is contrasted with higher frequency of group R1a chromosomes in the northern island of Krk and in the mainland. R1a frequency, while low in Greeks and Albanians, is highest in Polish, Ukrainian and Russian populations and could be a sign of the Slavic impact in the Balkan region. Haplogroups J, G and E that can be related to the spread of farming characterize the minor part (12.5%) of the Croatian paternal lineages. In one of the southern island (Hvar) populations, a relatively high frequency (14%) of lineages belonging to P\*(xM173) cluster was found, which is unusual for European populations. Interestingly, the same population also harbored mitochondrial haplogroup F that is virtually absent in European populations—indicating a connection with Central Asian populations, possibly the Avars.

**Marić I, Poljak L, Zoričić S, Bobinac D, Bosukonda D, Sampath KT, et al. Bone morphogenetic protein-7 reduces the severity of colon tissue damage and accelerates the healing of inflammatory bowel disease in rats. J Cell Physiol 2003;196:258-64.**

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Bone morphogenetic protein-7 (BMP-7) is a growth and differentiation factor and belongs to the TGF-beta superfamily of proteins. Previous studies have shown an abundant expression of BMP-7 in the developing intestine and an association with a perturbed BMP/SMAD downstream signaling leading to a malignant phenotype and inflammation in the gut. In the present study, the authors have evaluated the effect of systemically administered recombinant human BMP-7 against trinitrobenzenesulfonic (TNBS) acid induced inflammatory bowel disease (IBD) in rats. The TNBS administered rats treated with BMP-7 have developed much less severe form of colitis based on macroscopic and histological scoring when administered 1.5 h before or 24 h after colitis induction. Bioavailability studies in

healthy rats have revealed that significant portion (3.6%) of i.v. administered BMP-7 is targeted for BMP-7 receptors in the stomach and ileum, respectively, suggesting its availability to target tissue upon administration. Immunohistochemical and RT-PCR analyses have shown elevated expression of pro-inflammatory (IL-6, TNF-beta, ICAM-1) and pro-fibrogenic (TGF-beta) cytokines, and BMP-7 treatment significantly reduced their expression in the intestine; among which the suppression of IL-6 appeared to be the most important. Taken together, the results of this study suggest that BMP-7 plays an important role in the regulation of anti-inflammatory response in the adult gut tissue.

**Vraneš J, Kružić V, Šterk-Kuzmanović N, Schonwald S. Virulence characteristics of Escherichia coli strains causing asymptomatic bacteriuria. Infection 2003;31:216-20.**

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The objective of this study was to examine the expression of Escherichia coli virulence-associated factors among the strains isolated from a group of women with a history of recurrent urinary tract infections (UTIs), in whom asymptomatic bacteriuria (ABU) was detected at follow-up, and from a group of children without a history of previous UTI, in whom ABU was detected during the screening. Possible differences between the virulence potential of these strains were investigated. Hemolysin production, the ability to adhere to Buffalo green monkey cell line and hemagglutination (HA) ability of the ABU-associated E. coli strains were tested. E. coli strains isolated from patients with acute recurrent UTIs served as a comparison. The well-known low virulence of strains isolated from patients with ABU was demonstrated. In contrast to strains isolated from recurrent uncomplicated UTIs, the ABU-associated strains were mostly nonhemolytic (75%), nonadherent (70%) and lacked HA ability (61%). HA ability was significantly more common among the strains isolated from children without a history of UTI than among the strains isolated from women with recurrent UTIs ( $p < 0.01$ ), whereas the adherence and hemolytic abilities did not differ between the two ABU groups. A further prospective study is needed to determine whether the HA ability is the predictor of subsequent symptomatic UTI.

**Fatović-Ferenčić S. The history of medicine teaching program in Croatia. Acad Med 2003;78:1028-30.**

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A history of medicine program was first introduced at the University of Zagreb, Croatia, in 1927 by the internist Lujo Thaller, who became the first lecturer on this subject at Zagreb. However, the development of the program did not go smoothly and medicohistorians in Croatia were engaged in a constant struggle for proper status and a permanent place for their program within the medical school curriculum. Today a 15-hour medical history course (offered in the last semester of the 6-year curriculum) is mandatory at all four Croatian medical schools. The course draws on historical, cultural, sociological, epistemological, and bioethical aspects of medicine, with the goal of broadening students' perspectives on the practice of medicine and thereby enabling them to better meet the demands they will face as practicing physicians.