

Radman I, Bašić N, Labar B, Kovačević J, Aurer I, Bogdanić V, et al. Long-term results of conventional-dose salvage chemotherapy in patients with refractory and relapsed Hodgkin's disease (Croatian experience). *Ann Oncol* 2002;13:1650-5.

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The aim of this study was to analyze outcome of patients with Hodgkin's disease (HD) in whom first-line chemotherapy with mustine/vincristine/procarbazine/prednisone (MOPP) had failed. From January 1982 to December 1989 among 210 patients treated with MOPP and radiotherapy to initial bulky sites, 65 patients were primary refractory to or relapsed after initial treatment. Twenty-nine of 65 patients (44%) were primary refractory to initial chemotherapy, 20 relapsed within 12 months after complete remission (CR) and 16 relapsed after CR that lasted more than 12 months. Patients with primary refractory HD and early relapse (< 12 months after CR) were treated with doxorubicin/bleomycin/vinblastine/dacarbazine. In patients with late relapse (> 12 months after CR) MOPP was repeated. The median follow-up for all patients was 115 months. The overall response rate was 63%. Thirty-three patients (51%) achieved a second CR and eight patients (12%) partial response. Remission rate was greatest in patients with late relapse (CR > 12 months) (75 versus 55% for early relapse versus 35% for primary refractory HD) ($p < 0.01$). At 10 years, overall and failure-free survival rates were 21% and 16%, respectively. Patients who were in first remission longer than 12 months had a superior overall survival (37% versus 18% for early relapse) and failure-free survival (24% versus 10% for early relapse). No patient with primary refractory HD was alive beyond 52 months after initial treatment failure ($p < 0.01$). Main prognostic factors were duration of the first remission and tumor bulk at relapse. These results confirm previous observations that a significant proportion of patients with HD who experience induction treatment failure cannot be cured with conventional treatment and probably need more aggressive therapy.

Gong Y, Tagawa Y, Lunn MP, Laroy W, Heffer-Lauc M, Li CY, et al. Localization of major gangliosides in the PNS: implications for immune neuropathies. *Brain* 2002;125(Pt 11):2491-506.

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Antibodies targeting major gangliosides that are broadly distributed in the nervous system are sometimes associated with clinical symptoms that imply selective nerve damage. For example, anti-GD1a antibodies are associated with acute motor axonal neuropathy (AMAN), a form of Guillain-Barre syndrome that selectively affects motor nerves, despite reports that GD1a is present in human axons and myelin and is not expressed differentially in motor versus sensory roots. The authors used a series of high-affinity monoclonal antibodies (mAbs) against the major nervous system gangliosides GM1, GD1a, GD1b and GT1b to test whether any of them binds motor or sensory fibres differentially in rodent and human peripheral nerves. The following observations were made: 1) some of the anti-GD1a antibodies preferentially stained motor fibres, supporting the association of human anti-GD1a antibodies with predominant mo-

tor neuropathies such as AMAN; 2) a GD1b antibody preferentially stained the large dorsal root ganglion (DRG) neurones, in keeping with the proposed role of human anti-GD1b antibodies in sensory ataxic neuropathies; 3) two mAbs with broad structural cross-reactivity bound to both gangliosides and peripheral nerve proteins; 4) myelin was poorly stained; all clones stained axons nearly exclusively. These findings suggest that anti-ganglioside antibody fine specificity as well as differences in ganglioside accessibility in axons and myelin influence the selectivity of injury to different fibre systems and cell types in human autoimmune neuropathies.

Šustić A, Krstulović B, Eškinja N, Zelić M, Ledić D, Turina D. Surgical tracheostomy versus percutaneous dilational tracheostomy in patients with anterior cervical spine fixation: preliminary report. *Spine* 2002;27:1942-5 (discussion: 1945).

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The aim of this study was to compare the incidence of perioperative and early postoperative complications of surgical tracheostomy (ST) vs. ultrasound-guided percutaneous dilational tracheostomy (PDT) in patients with anterior cervical spine fixation (ACSF). Sixteen adult patients who underwent tracheostomy after acute spinal cord injury and ACSF were analyzed. The patients were randomly assigned to two groups: eight patients (six males; age range, 24-59 years) who underwent ST and eight patients (seven males; age range, 19-47 years) who underwent ultrasound-guided PDT with dilational forceps technique. The incidence of peri- and early postoperative complications was followed up, as well as the stoma infections and the duration of the procedure. Not one patient from either group had any major perioperative complication of tracheostomy. In each group, there was one case of prolonged bleeding, which stopped spontaneously inside 24 hours. In two patients (25%) from the ST group, purulent infection of the stoma was verified during subsequent treatment at an intensive care unit. The average time of ST was 21 ± 7 minutes; the average time of ultrasound-guided PDT was 8 ± 6 minutes ($p < 0.05$). These preliminary data demonstrate that ultrasound-guided PDT as regards to complications is at least equally safe as ST; at the same time, it is much quicker method, probably with less late infections of the stoma, which could be an important advantage in patients with ACSF.

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 = 55.7 years. The subjects were divided into 2 groups: 1 group – coronary artery disease (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.

Višnjić D, Črljen V, Čurić J, Batinić D, Volinia S, Banfić H. The activation of nuclear phosphoinositide 3-kinase C2beta in all-trans-retinoic acid-differentiated HL-60 cells. FEBS Lett 2002; 529:268-74.

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The activity of nuclear phosphoinositide 3-kinase C2beta (PI3K-C2beta) was investigated in HL-60 cells induced to differentiate along granulocytic or monocytic lineages. A significant increase in the activity of immunoprecipitated PI3K-C2beta was observed in the nuclei and nuclear envelopes isolated from all-trans-retinoic acid (ATRA)-differentiated cells which was inhibited by the presence of PI3K inhibitor LY 294002. High-performance liquid chromatography analysis of inositol lipids showed an increased incorporation of radiolabelled phosphate in both PtdIns(3)P and PtdIns(3,4,5)P(3) with no changes in the levels of PtdIns(4)P, PtdIns(3,4)P(2) and PtdIns(4,5)P(2). Western blot analysis of the PI3K-C2beta immunoprecipitates with anti-P-Tyr antibody revealed a significant increase in the level of the immunoreactive band corresponding to PI3K-C2beta in the nuclei and nuclear envelopes isolated from ATRA-differentiated cells.

Vrhovac B. Conflict of interest in Croatia: doctors with dual obligations. Sci Eng Ethics 2002;8:309-16.

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There is an emerging awareness of the possibility of conflicts of interest in the practice of medicine in Croatia. The paper examines areas within the medical profession where conflicts of interest can and have occurred, probably not only in Croatia. Particularly addressed are situations when a doctor may have dual obligations and how independent ethics committees can help in decreasing the influence of a conflict of interest. The paper also presents extracts from the Croatian Code of Ethics for the medical profession that address problems of conflict of interest.

Peričić D, Šob D. Interaction of stress and noradrenergic drugs in the control of picrotoxin-induced seizures. Epilepsy Res 2002;51:179.

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To evaluate the possible role of noradrenergic system in the anticonvulsant effect of swim stress, the mice were prior to exposure to swim stress and the i.v. infusion of picrotoxin, pre-treated with desipramine (a noradrenaline reuptake inhibitor), N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine (DSP-4, a neurotoxin which destructs noradrenergic axons) or alpha-methyl-p-tyrosine (alpha-MPT, an inhibitor of catecholamine synthesis) and the latency to the onset of two convulsant signs and death was registered. While in control unstressed animals desipramine (20 mg/kg i.p.) and alpha-MPT (200 mg/kg i.p.) failed to affect, DSP-4 (50 mg/kg i.p., given 3 weeks prior to experiment) tended to decrease the dose of picrotoxin needed to produce tonic hindlimb extension (THE) and death. Swim

stress prolonged the latency, i.e. increased (64-116% above control) the dose of picrotoxin needed to produce convulsant signs and death. In swim stressed mice desipramine enhanced the doses of picrotoxin needed to produce running-bouncing clonus (RB clonus), THE and death. alpha-MPT and DSP-4 pre-treatment failed to prevent the anticonvulsant effect of stress. Moreover, the effect of stress was greater in DSP-4 pre-treated mice. Although further studies are needed, the results suggest that the integrity of noradrenergic system is not substantial for the anticonvulsant effect of stress.

Orešković D, Klarica M, Vukić M. The formation and circulation of cerebrospinal fluid inside the cat brain ventricles: a fact or an illusion? Neurosci Lett 2002;327:103-6.

Department of Molecular Genetics, Laboratory of Neurochemistry and Molecular Neurobiology, Ruđer Bošković Institute, Zagreb, Croatia

Formation and circulation of cerebrospinal fluid (CSF) have been studied in the isolated brain ventricles of anesthetized cats by a new approach and under direct observation. A plastic cannula was introduced into the aqueduct of Sylvius through the vermis cerebelli and the outflow of CSF from the cannula was used as the CSF formation and circulation index. During the 60 min of observation at a physiological CSF pressure not a single drop of CSF escaped out of the end of the cannula. This indicates that CSF net formation and circulation inside the brain ventricles, proposed by classical hypothesis regarding CSF dynamics, should be at least re-evaluated.

Vukšić M, Petanjek Z, Rasin MR, Kostović I. Perinatal growth of prefrontal layer III pyramids in Down syndrome. Pediatr Neurol 2002;27:36-8.

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The authors analyzed the dendritic differentiation of layer IIIc pyramidal neurons of prefrontal cortex (prospective area 9) in the brains of a premature infant and a 2.5-month-old infant with Down syndrome and two age-matched control subjects during the peak period of dendritic growth and differentiation. Quantitative analysis supports qualitative observation and revealed no significant differences in the tempo and mode of dendritic differentiation between normal and Down syndrome cases. The authors have concluded that the children with Down syndrome from this study begin their lives with morphologically normal layer III pyramidal neurons. The findings suggest that pathologic changes of key prefrontal input-output neuronal elements begin to develop in Down syndrome after 2.5 months of postnatal age.

Grubišić-Ilić M, Kozarić-Kovačić D, Grubišić F, Kovačić Z. Epidemiological study of suicide in the Republic of Croatia – comparison of war and post-war periods and areas directly and indirectly affected by war. Eur Psychiatry 2002;17:259.

Department of Applied Psychology and Forensic Medicine, Police Academy, Zagreb, Croatia

The authors examined the differences in the suicide characteristics between areas directly and indirectly affected by war activities and in war and post-war periods according to the following variables: suicide rate, sex, age and method of suicide. Analysis was done on 5349 suicides committed in the period 1993-1998 (war and post-war years). The suicide rates in the Republic of Croatia oscillated in the pre-war, war and post-war periods (1985-2000) but without significant differences. In the areas directly affected by war, the suicide rate was significantly lower than in other areas during the study period 1993-1998 (chi-square = 10.3245; $p = 0.0017$). The number of suicides in both sexes declined in the areas directly affected by war - more in men than in women; the difference between sexes was statistically significant (chi-square = 3.6697; $p = 0.055$). Middle- and old-aged people were the population with high suicide risk in both areas ($t = 1.76$; $p = 0.078$). There were significant differences in the methods of suicides between war and non-war ar-

eas (chi-square = 108.8473; $p = 0.001$). Firearms or explosive devices were the methods used more significantly for suicides in the areas directly affected by war than in other areas, whereas hanging was more frequently used in the areas indirectly affected by war.

Piasek M, Laskey JW, Kostial K, *Blanuša M. Assessment of steroid disruption using cultures of whole ovary and/or placenta in rat and in human placental tissue. *Int Arch Occup Environ Health* 2002;75 Suppl 1:36-44.

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The paper presents results of collaborative research on cadmium as an endocrine disruptor. To detect steroidogenic alterations in cycling and pregnant rats following cadmium exposures in vivo (at 3 or 5 mg/kg as a single s.c. dose) and in vitro (from 0 through 2,000 micromolar Cd^{2+} whole-ovary culture was used. To evaluate steroid productions in rats fed low iron (10 ppm) and concomitantly exposed to cadmium (5 mg/kg total dose by s.c.-implanted osmotic pumps) during 19 days of pregnancy whole-placenta culture was also used. In human placental tissue cadmium and progesterone concentrations were assessed in relation to cigarette smoking. Cultures of minced ovaries were evaluated for 1-h basal steroid production and following 1-h production stimulated with either human chorionic gonadotropin (hCG) or hCG and pregnenolone. Placental cultures were evaluated for average 1-h progesterone production following 3 h of unstimulated production. In-vivo cadmium exposure interfered with normal steroidogenesis in cycling rats and in early pregnancy, with ovarian estradiol production the most affected. Under in-vitro cadmium exposure the most affected was ovarian production of progesterone and testosterone in cycling (proestrous) rats with medial inhibitory concentrations under 500 micromolar Cd^{2+} . Cadmium interfered with the steroidogenic pathway at more than one site. Linear and additive effects of low-iron feeding and concomitant cadmium exposure during pregnancy on placental progesterone production were found. In humans, we found that the placentas of smoking mothers contained twice as much cadmium and approximately half the amount of progesterone than did the placentas of non-smoking mothers. Results of the research on cadmium-induced steroidogenic effects using cultures of whole rat ovary and/or placenta as well as human placental tissues point to cadmium as an endocrine disruptor that may compromise pregnancy outcome and fetal viability.

Halassy-Špoljar B, Cimborja T, Hanzl-Dujmović I, Dojnović B, Sabioncello A, Krstanović M, et al. Influence of adjuvant-active peptidoglycan monomer on specific T cell responses in mice. *Vaccine* 2002;20:3543.

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Peptidoglycan monomer (PGM) originating from *Brevibacterium divaricatum* is a non-toxic, non-pyrogenic, water-soluble immunostimulator. It potentiates humoral immune response to ovalbumin (OVA) in mice upregulating both immunoglobulin (IgG) 1 and IgG2a antibody subclasses. This study concerns the influence of PGM on T cell activation and cytokine networks in response to OVA. OVA-specific proliferative response as well as interferon-gamma (IFN-gamma) and interleukin-4 (IL-4) secretion in lymph node cell cultures of immunised mice were studied. Due to pharmacokinetic properties of PGM, namely its fast metabolism and excretion, special emphasis was on choosing the appropriate time for lymph node removal and duration of cell cultivation for each cytokine. PGM treatment in addition to OVA resulted in an increase of lymph node cellularity, stimulation of OVA-specific IFN-gamma and IL-4 production as well as of OVA-specific proliferative response. Results demonstrate that PGM stimulated both Th1 and Th2 subpopulations.

Grgić M, Ivkić M. Use of skin staplers in head and neck surgery: prospective clinical study. *J Otolaryngol* 2002;31:137-9.

Department of Otorhinolaryngology and Head and Neck Surgery, University Hospital Sestre Milosrdnice, Zagreb, Croatia

The aim of this study was to compare the advantages and disadvantages of skin staplers versus conventional sutures in head and neck surgery. Fifty consecutive patients who underwent extensive surgery in the head and neck area were included in this prospective trial. Patients were randomized into two equal groups: one group had their wounds closed with staplers and the other with monofilament sutures. The main outcome measures were speed of suturing, wound healing and cosmetic result, complications, and cost of either method. Cosmetic results were good in both groups. Neither group had any complications. Wound closure speed was 18.9 ± 1.4 cm/min when using skin staplers and 1.9 ± 0.4 cm/min for conventional suturing ($p < 0.001$). In conclusion, skin staplers significantly reduce wound closure time and yield similar cosmetic results with no complications and with only a slightly higher cost of suturing material.

Martin-Kleiner I, Gabrilovac J. The kappa-opioid agonist U-69593 affects intracellular calcium level in R1.1 mouse thymoma cell line. *Int Immunopharmacol* 2002;2:975-80.

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In this study, the effect of the kappa-opioid agonist U-69593 on the intracellular calcium level in R1.1 cells was investigated using FURA 2-AM dye. In the previous study, calcium transport into R1.1 cells was not affected by the kappa-opioid agonist U50,488. In this study, the kappa-opioid agonist U-69593 (10^{-10} - 10^{-6} M), decreased intracellular calcium level in unstimulated cells. This decrease could not be reversed by the kappa-opioid antagonist NBI (10^{-5} or 10^{-6} M). Ionophore A23187 was used to increase intracellular calcium level. Stimulation of intracellular calcium level by ionophore A23187 was potentiated by the kappa-opioid agonist U-69593. Thus, it has been shown that basal intracellular calcium level is decreased in R1.1 by the kappa-opioid agonist U-69593 and increased in R1.1 cells stimulated by ionophore A23187.

Orešković S, Božičević I, Mastilica M, Bakran I, Popović SG, Ben-Joseph R. Health-care resource use by asthmatics in Croatia. *J Asthma* 2002;39:351-8.

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The authors report a survey of the impact of asthma on daily life and on health-care resource use by adult asthma patients in four counties in Croatia. Over a 1-year period beginning November 1998, 185 general practitioners recruited 504 asthma patients, who completed a questionnaire about their drug therapy, health-care resource use, symptoms, limitations in daily activities, and work loss due to asthma. Over a 2-week period, inhaled corticosteroids were used by 51.5% of patients, short-acting and long-acting beta-agonists by 70.8% and 53.5%, respectively, and oral extended-release theophyllines by 29.8%. Nocturnal awakenings were experienced by 58.7% of patients, 75.5% experienced daytime symptoms, and 42.5% were limited in their daily activities. In the previous year, 12.5% of the patients were hospitalized, 33% missed work, and 70% reported reduced effectiveness in the workplace. In the previous 6 months, 35.2% of the patients visited an emergency room due to worsening of asthma symptoms. The human and socio-economic burden of asthma in Croatia is considerable. These results can help guide the development of asthma policy in Croatia and raise awareness of asthma as a public health issue.